PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 April 2001 (04.04.01)	
International application No. PCT/EP00/06769	**Applicant's or agent's file reference** HMR99L044/PCT
International filing date (day/month/year) 15 July 2000 (15.07.00)	**Priority date** (day/month/year) 27 July 1999 (27.07.99)
Applicant BANSI, Lal et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

15 February 2001 (15.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

DL = 05-04-01

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
HOECHST MARION ROUSSEL
Département des Brevets
Attn. VIEILLEFOSSE, J.
102, Route de Noisy
F - 93235 Romainville Cedex
FRANCE

Hoechst Marion Roussel
05. FEV. 2001
DEPARTEMENT DES BREVETS

Date of mailing *(day/month/year)* 05/02/2001	
Applicant's or agent's file reference HMR99L044/PCT	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/EP 00/06769	International filing date *(day/month/year)* 15/07/2000
Applicant AVENTIS PHARMA DEUTSCHLAND GMBH	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Carla Louro

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 February 2001 (01.02.2001)

PCT

(10) International Publication Number
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(21) International Application Number: PCT/EP00/06769

(22) International Filing Date: 15 July 2000 (15.07.2000)

(25) Filing Language: English

(26) Publication Language: English

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99114649.9 27 July 1999 (27.07.1999) EP

(71) Applicant *(for all designated States except US)*: AVENTIS PHARMA DEUTSCHLAND GMBH [DE/DE]; Brüningstrasse 50, D-65929 Frankfurt am Main (DE).

(72) Inventors; and

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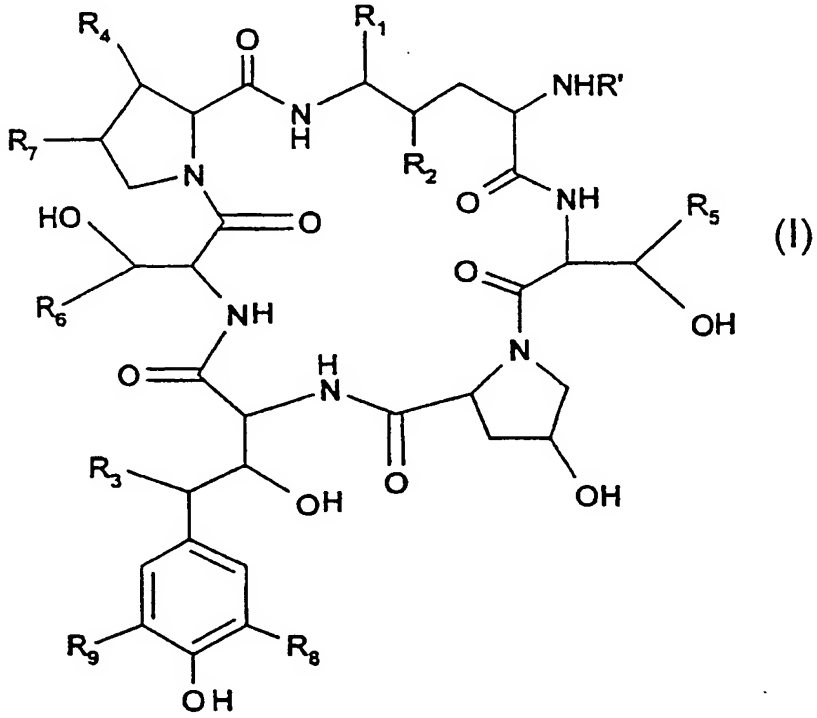
(81) Designated States *(national)*: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian

[Continued on next page]

(54) Title: NOVEL CYCLOHEXAPEPTIDE COMPOUNDS, PROCESSES FOR THEIR PRODUCTION AND THEIR USE AS A PHARMACEUTICAL



(I)

(57) Abstract: A cyclohexapeptide compound of general formula (I), wherein R^1 is C_1-C_{20} alkyl; C_9-C_{20} alkenyl; C_9-C_{20} alkoxyphenyl; an aryl group selected from: phenyl, biphenyl, terphenyl and naphthyl; C_1-C_{12} alkylphenyl, C_2-C_{12} alkenylphenyl, C_1-C_{12} alkoxyphenyl; linoleoyl; palmitoyl; 12-methylmyristoyl; 10,12-dimethylmyristoyl; or $-COC_6H_4(p)OC_8H_{17}$, R_1 and R_3 are independently -OH; -CN; $-CH_2NH_2$; $-N_3$; aryl; substituted aryl; heterocyclyl and substituted heterocyclic with 1-3 of the same or different heteroatoms; aminoalkylamino; mono or di-substituted linear or cyclic aminoalkylamino; -OR, wherein, R is C_1-C_{12} alkyl; substituted alkyl of the type $-(CH_2)_n$-X, where n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2 or a heterocyclic and where Y is C_1-C_6 linear or branched alkyl; C_2-C_{12}-alkenyl; aryl; fused aryl; substituted aryl; a heterocyclic containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group; and R_3 may additionally be imidazolyl; R_2 and R_4 are independently -H or -OH; R_5 is -H or $-CH_3$. R_6 is -H, $-CH_3$ or $-CH_2CONH_2$. R_7 is -H, $-CH_3$ or -OH. R_8 and R_9 are independently -H or $-CH_2$-Sec.amine in which the sec.amine is attached to $-CH_2$ through its N linkage; and its pharmaceutically acceptable salts. The compounds are useful as antifungal agents.

WO 01/07468 A2

patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
HMR99L044/PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06769	15/07/2000	27/07/1999
International Patent Classification (IPC) or national classification and IPC C07K7/56		
Applicant AVENTIS PHARMA DEUTSCHLAND GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/02/2001	15.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Groenendijk, M Telephone No. +31 70 340 3715

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06769

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

   1-59 as originally filed

   Claims, No.:

   1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,9
	No:	Claims	1-4,6-8,10
Inventive step (IS)	Yes:	Claims	5,9
	No:	Claims	1-4,6-8,10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item IV
Lack of unity of invention

This International Examining Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 4,5,9(all complete),1-3,7,8(all partially)

   Compounds according to formula I, wherein at least one of R8 and R9 is -CH2-sec-amine, their preparation and pharmaceutical compositions.

2. Claims: 6,10(complete)1-3,7,8(all partially)

   Compounds according to formula I, wherein R8 and R9 are both H, their preparation and pharmaceutical compositions.

Reasoning

1)Reading the claims in the light of the description the problem to be solved could initially be considered to be the provision of compounds having antifungal activity.
2)This problem has been solved by a plurality of solutions as defined in claim 1, relating to cyclohexapeptides of the echinocandin type. The application further relates to pharmaceutical compositions containing said compounds, their preparation and use.
3)This plurality of solutions might, a priori, be considered as satisfying the requirements of unity in which the antifungal activity provides the special technical feature linking these different solutions.
4)However at the first priority date of the application compounds having antifungal activity were already well-known in the prior art, as can be exemplified by the documents cited in the ISR and which can be illustrated by WO9527074 (D1).
5)In the light of these documents, it is considered that a common technical link based on the antifungal activity exhibited by the compounds of the application which could be the unifying concept is no longer present.
6)The objective problem in view of D1 could therefore be considered to be the provision of alternative compounds having antifungal activity.

7)Therefore further unified solutions should relate to groups of compounds sharing a common structural element which may be regarded as the special technical feature providing unity; this special technical feature should be an essential structural part common to all of the embodiments of the claimed invention (and responsible for the inventive effect) and which is absent from any solution to the same problem disclosed in the prior art.
8)Regarding all of the proposed solutions as a whole, as defined in independent claim 1, the only common invariant structural features which can be detected are the structure of general formula I, disregarding the variable substituents R1-R9 and R'.
9)It is considered that D1 discloses compounds which possess the same structural features as those described above and are intended for the solution of the same problem as that underlying the present application. For these reasons it is considered that the compounds claimed in the present application lack any common structural feature which could be regarded as the special technical feature providing unity to the application.
10)As no other technical features can be distinguished which, in the light of the prior art, could be considered as special technical features on which a unifying concept could be based, there is lack of unity between the plurality of claimed inventions defined in the compound claims of the present application (see Rule 13.1 PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1:WO-A-9527074
D2:J.Antibiot., Vol. XL, No.3, 275-280
D3:WO-A-9622784
D4:WO-A-9421677
D5-US-A-5914313

1)subj.1

I.NOVELTY

D1 discloses cyclohexapeptides of the present type which are characterized, inter alia, by the presence of at least one disubstituted aminoalkyl group as substituent in the tyrosine ring (see especially claim 1, substituent R8). The examiner is guided by the principle according to which the disclosure in a prior document likely to affect the novelty of a claim is not necessarily limited to the specific working examples, but also comprises any reproducible technical teaching described in the document. In order to acknowledge novelty to the not specifically disclosed overlapping subject-matter it is considered to be necessary that said subject-matter is based on a new technical teaching. It is at present not apparent whether the subject-matter of the overlapping area relates to a new technical teaching (based on a new "technical element") with respect to the prior art and therefore novelty cannot be recognised for said overlapping area. Consequently the claims 1-4,7 and 8 are considered to lack novelty under Art.33(2) PCT.

II.INVENTIVE STEP

1)The closest prior art is considered to be D1 disclosing, as discussed in the previous section, cyclohexapeptides of the present type which are characterized, inter alia, by the presence of at least one disubstituted aminoalkyl group as substituent in the tyrosine ring (see especially claim 1, substituent R8).

2)The novel subject-matter of the present application essentially differs from said prior art in the presence of a cyclic secondary aminomethyl group as substituent of the tyrosine ring. Said compounds exhibit antifungal activity and have a good water solubility.

3)The problem to be solved may therefore be considered to be the provision of alternative antifungal compounds having a cyclopeptide structure and a good solubility in water.

4)It is considered that in the prior art the present cyclic secondary aminoalkyl group as substituent of the tyrosine ring neither has been indicated nor suggested.

5)Consequently an inventive step can be acknowledged under Art.33(3) PCT for the subject-matter of claim 5 and also for their production process as defined in claim 9.

2. subj.

I.NOVELTY

1)D2 discloses the basic compound Mulundocandin, wherein the positions corresponding to R1 and R3 in the general formula I of the application are both hydroxy. Hence the claims 1-3 and 6-8 lack novelty under Art.33(2) PCT.

2)D3 discloses cyclohexapeptides encompassed by the present formula I, which are characterized, inter alia, by a facultative substituted aminomethyl group or a nitril group in the corresponding position R1 and a sidechain R' which can comprise a C9-C21 alkyl group. Furthermore the process for preparing said compounds (e.g., see pages 11-12) includes the steps a-c of claim 10.

The examiner is guided by the principle according to which the disclosure in a prior document likely to affect the novelty of a claim is not necessarily limited to the specific working examples, but also comprises any reproducible technical teaching described in the document. In order to acknowledge novelty to the not specifically disclosed overlapping subject-matter it is considered to be necessary that said subject-matter is based on a new technical teaching. It is at present not apparent whether the subject-matter of the overlapping area relates to a new technical teaching (based on a new "technical element") with respect to the prior art and therefore novelty cannot be recognised for said overlapping area. Consequently the claims 1-3,6-8 and 10 are considered to lack novelty under Art.33(2) PCT.

3)Document D4 relates to cyclohexapeptides of the present type, comprising in position R1 a substituted amino group. In view of this prior art the claims 1-3 and 6-8 are considered not to fulfil the requirements of Art.33(2) PCT.

4)D5 also discloses cyclohexapeptides, which in this document are characterized by a substituted alkyloxy group in position R1. For reasons mentioned in the preceding part D5 renders the claims 1-3,6-8 not novel under Art.33(2) PCT.

Re Item VII

Certain defects in the international application

In order to meet the requirements of Rule 5.1(a)(ii) PCT the documents D1-D5 should have been discussed in the description.

Re Item VIII

Certain observations on the international application

1)An independent claim should clearly specify all of the essential features needed to define the invention PCT Guidelines C-III,4.1-4.7a). The present claims 1,2,4,6,9 and 10 contain expressions like "(substituted) aryl" and "(substituted) heterocycle", rendering the scope of said claims unclear under Art.6 PCT. It is true that under circumstances such expressions can be acceptable in product claims, e.g. in definitions of non- essential features like protecting groups. However in the present case said expressions are also used to define structural features that are considered to be characteristic for the present compounds. Consequently the claims 1,2,4,6,9 and 10 are considered not to fulfil the requirements of Art.6 PCT.

2)The claims should be supported by the description (PCT Guidelines CIII,6.1-6.6). That is, the claims should be a fair generalization over the experimental data. However at present the examples comprise only a very small part of the compounds claimed, which part is moreover not evenly distributed over the whole claimed area, whereas even any experimental data relating to their activity is lacking.

Consequently the claims 1-10 are considered to contravene Art.6 PCT.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
HMR99L044/PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/06769	15/07/2000	27/07/1999
Applicant		
AVENTIS PHARMA DEUTSCHLAND GMBH		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/06769

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 4,5,9(all complete),1-3,7,8(all partially)

   Compounds according to formula I, wherein at least one of R8 and R9 is -CH2-sec-amine, their preparation and pharmaceutical compositions.

2. Claims: 6,10(complete)1-3,7,8(all partially)

   Compounds according to formula I, wherein R8 and R9 are both H, their preparation and pharmaceutical compositions.

   The applicant's attention is drawn to the fact that a search for this subject could result in a further declaration of lack of unity (within this group)

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 00/06769

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K7/56 A61K38/12 A61P31/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, PAJ, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 27074 A (MERCK & CO INC) 12 October 1995 (1995-10-12) the whole document ---	1-5,7,8
A	WO 96 11210 A (FUJISAWA PHARMACEUTICAL CO ;OHKI HIDENORI (JP); TOMISHIMA MASAKI () 18 April 1996 (1996-04-18) the whole document --- -/--	1-5,7,8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 January 2001	05. 02. 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Groenendijk, M

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 00/06769

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	"SYNTHESIS, STABILITY, AND BIOLOGICAL EVALUATION OF WATER-SOLUBLE PRODRUGS OF A NW ECHINOCANDIN LIPOPEPTIDE. DISCOVERY OF A POTENTIAL CLINICAL AGENT FOR THE TREATMENT OF SYSTEMIC CANDIDIASIS AND PNEUMOCYSTIC CARINII PNEUMONIO (PCP)" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 35, no. 1, 10 January 1992 (1992-01-10), pages 194-198, XP000571471 ISSN: 0022-2623 See especially Table 1 ---	1-5,7,8
X	ROY E.A.: "Mulundocandin, a new lipopeptide antibiotic" JOURNAL OF ANTIBIOTICS., vol. XL, no. 3, March 1987 (1987-03), pages 275-280, XP002129427 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820 the whole document ---	1-3,6-8
X	WO 96 22784 A (MERCK & CO INC ;BOUFFARD FRANCES A (US)) 1 August 1996 (1996-08-01) page 12 -page 13; claims 1-4,13-19; examples 1-4 ---	1-3,6-8, 10
X	WO 94 21677 A (BOUFFARD FRANCES AILEEN ;BLACK REGINA M (US); MERCK & CO INC (US);) 29 September 1994 (1994-09-29) the whole document ---	1-3,6-8
X	US 5 914 313 A (BOUFFARD FRANCES AILEEN ET AL) 22 June 1999 (1999-06-22) the whole document -----	1-3,6-8

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PC[redacted]P 00/06769

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9421677 A		ZA 9401807 A	13-10-1994
US 5914313 A	22-06-1999	AT 140460 T	15-08-1996
		CA 2080756 A	18-04-1993
		DE 69212267 D	22-08-1996
		DE 69212267 T	30-01-1997
		EP 0539088 A	28-04-1993
		JP 5239095 A	17-09-1993
		AU 5354094 A	09-05-1994
		WO 9409033 A	28-04-1994

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
HMR99L044/PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06769	15/07/2000	27/07/1999
International Patent Classification (IPC) or national classification and IPC C07K7/56		
Applicant AVENTIS PHARMA DEUTSCHLAND GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
VI	☐	Certain documents cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/02/2001	15.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Groenendijk, M Telephone No. +31 70 340 3715

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06769

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-59 as originally filed

Claims, No.:

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,9
	No:	Claims	1-4,6-8,10
Inventive step (IS)	Yes:	Claims	5,9
	No:	Claims	1-4,6-8,10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item IV
Lack of unity of invention

This International Examining Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 4,5,9(all complete),1-3,7,8(all partially)

   Compounds according to formula I, wherein at least one of R8 and R9 is -CH2-sec-amine, their preparation and pharmaceutical compositions.

2. Claims: 6,10(complete)1-3,7,8(all partially)

   Compounds according to formula I, wherein R8 and R9 are both H, their preparation and pharmaceutical compositions.

Reasoning
1)Reading the claims in the light of the description the problem to be solved could initially be considered to be the provision of compounds having antifungal activity.
2)This problem has been solved by a plurality of solutions as defined in claim 1, relating to cyclohexapeptides of the echinocandin type. The application further relates to pharmaceutical compositions containing said compounds, their preparation and use.
3)This plurality of solutions might, a priori, be considered as satisfying the requirements of unity in which the antifungal activity provides the special technical feature linking these different solutions.
4)However at the first priority date of the application compounds having antifungal activity were already well-known in the prior art, as can be exemplified by the documents cited in the ISR and which can be illustrated by WO9527074 (D1).
5)In the light of these documents, it is considered that a common technical link based on the antifungal activity exhibited by the compounds of the application which could be the unifying concept is no longer present.
6)The objective problem in view of D1 could therefore be considered to be the provision of alternative compounds having antifungal activity.

7)Therefore further unified solutions should relate to groups of compounds sharing a common structural element which may be regarded as the special technical feature providing unity; this special technical feature should be an essential structural part common to all of the embodiments of the claimed invention (and responsible for the inventive effect) and which is absent from any solution to the same problem disclosed in the prior art.
8)Regarding all of the proposed solutions as a whole, as defined in independent claim 1, the only common invariant structural features which can be detected are the structure of general formula I, disregarding the variable substituents R1-R9 and R'.
9)It is considered that D1 discloses compounds which possess the same structural features as those described above and are intended for the solution of the same problem as that underlying the present application. For these reasons it is considered that the compounds claimed in the present application lack any common structural feature which could be regarded as the special technical feature providing unity to the application.
10)As no other technical features can be distinguished which, in the light of the prior art, could be considered as special technical features on which a unifying concept could be based, there is lack of unity between the plurality of claimed inventions defined in the compound claims of the present application (see Rule 13.1 PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1:WO-A-9527074
D2:J.Antibiot., Vol. XL, No.3, 275-280
D3:WO-A-9622784
D4:WO-A-9421677
D5-US-A-5914313

1)subj.1

I.NOVELTY

D1 discloses cyclohexapeptides of the present type which are characterized, inter alia, by the presence of at least one disubstituted aminoalkyl group as substituent in the tyrosine ring (see especially claim 1, substituent R8). The examiner is guided by the principle according to which the disclosure in a prior document likely to affect the novelty of a claim is not necessarily limited to the specific working examples, but also comprises any reproducible technical teaching described in the document. In order to acknowledge novelty to the not specifically disclosed overlapping subject-matter it is considered to be necessary that said subject-matter is based on a new technical teaching. It is at present not apparent whether the subject-matter of the overlapping area relates to a new technical teaching (based on a new "technical element") with respect to the prior art and therefore novelty cannot be recognised for said overlapping area. Consequently the claims 1-4,7 and 8 are considered to lack novelty under Art.33(2) PCT.

II.INVENTIVE STEP

1)The closest prior art is considered to be D1 disclosing, as discussed in the previous section, cyclohexapeptides of the present type which are characterized, inter alia, by the presence of at least one disubstituted aminoalkyl group as substituent in the tyrosine ring (see especially claim 1, substituent R8).

2)The novel subject-matter of the present application essentially differs from said prior art in the presence of a cyclic secondary aminomethyl group as substituent of the tyrosine ring. Said compounds exhibit antifungal activity and have a good water solubility.

3)The problem to be solved may therefore be considered to be the provision of alternative antifungal compounds having a cyclopeptide structure and a good solubility in water.

4)It is considered that in the prior art the present cyclic secondary aminoalkyl group as substituent of the tyrosine ring neither has been indicated nor suggested.

5)Consequently an inventive step can be acknowledged under Art.33(3) PCT for the subject-matter of claim 5 and also for their production process as defined in claim 9.

2. subj.

I.NOVELTY

1)D2 discloses the basic compound Mulundocandin, wherein the positions corresponding to R1 and R3 in the general formula I of the application are both hydroxy. Hence the claims 1-3 and 6-8 lack novelty under Art.33(2) PCT.

2)D3 discloses cyclohexapeptides encompassed by the present formula I, which are characterized, inter alia, by a facultative substituted aminomethyl group or a nitril group in the corresponding position R1 and a sidechain R' which can comprise a C9-C21 alkyl group. Furthermore the process for preparing said compounds (e.g., see pages 11-12) includes the steps a-c of claim 10.

The examiner is guided by the principle according to which the disclosure in a prior document likely to affect the novelty of a claim is not necessarily limited to the specific working examples, but also comprises any reproducible technical teaching described in the document. In order to acknowledge novelty to the not specifically disclosed overlapping subject-matter it is considered to be necessary that said subject-matter is based on a new technical teaching. It is at present not apparent whether the subject-matter of the overlapping area relates to a new technical teaching (based on a new "technical element") with respect to the prior art and therefore novelty cannot be recognised for said overlapping area. Consequently the claims 1-3,6-8 and 10 are considered to lack novelty under Art.33(2) PCT.

3)Document D4 relates to cyclohexapeptides of the present type, comprising in position R1 a substituted amino group. In view of this prior art the claims 1-3 and 6-8 are considered not to fulfil the requirements of Art.33(2) PCT.

4)D5 also discloses cyclohexapeptides, which in this document are characterized by a substituted alkyloxy group in position R1. For reasons mentioned in the preceding part D5 renders the claims 1-3,6-8 not novel under Art.33(2) PCT.

Re Item VII

Certain defects in the international application

In order to meet the requirements of Rule 5.1(a)(ii) PCT the documents D1-D5 should have been discussed in the description.

Re Item VIII

Certain observations on the international application

1)An independent claim should clearly specify all of the essential features needed to define the invention PCT Guidelines C-III,4.1-4.7a). The present claims 1,2,4,6,9 and 10 contain expressions like "(substituted) aryl" and "(substituted) heterocycle", rendering the scope of said claims unclear under Art.6 PCT. It is true that under circumstances such expressions can be acceptable in product claims, e.g. in definitions of non- essential features like protecting groups. However in the present case said expressions are also used to define structural features that are considered to be characteristic for the present compounds. Consequently the claims 1,2,4,6,9 and 10 are considered not to fulfil the requirements of Art.6 PCT.

2)The claims should be supported by the description (PCT Guidelines CIII,6.1-6.6). That is, the claims should be a fair generalization over the experimental data. However at present the examples comprise only a very small part of the compounds claimed, which part is moreover not evenly distributed over the whole claimed area, whereas even any experimental data relating to their activity is lacking.

Consequently the claims 1-10 are considered to contravene Art.6 PCT.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 February 2001 (01.02.2001)

PCT

(10) International Publication Number
WO 01/07468 A2

(51) International Patent Classification[7]: C07K 7/56, A61K 38/12, A61P 31/10

(21) International Application Number: PCT/EP00/06769

(22) International Filing Date: 15 July 2000 (15.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99114649.9 27 July 1999 (27.07.1999) EP

(71) Applicant *(for all designated States except US)*: AVENTIS PHARMA DEUTSCHLAND GMBH [DE/DE]; Brüningstrasse 50, D-65929 Frankfurt am Main (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BANSI, Lal [IN/IN]; 30, Advani Apartments, Mulund (West), Mumbai 400 080 (IN). VITTHAL, Genbhau, Gund [IN/IN]; K-1, Hoechst Quarters, Darga Road, Amarnagar, Mulund (West), Mumbai 400 080 (IN). ASHOK, Kumar, Gangopadhyay [IN/IN]; K-33, Hoechst Quarters, Darga Road, Amarnagar, Mulund (West), Mumbai 400 080 (IN).

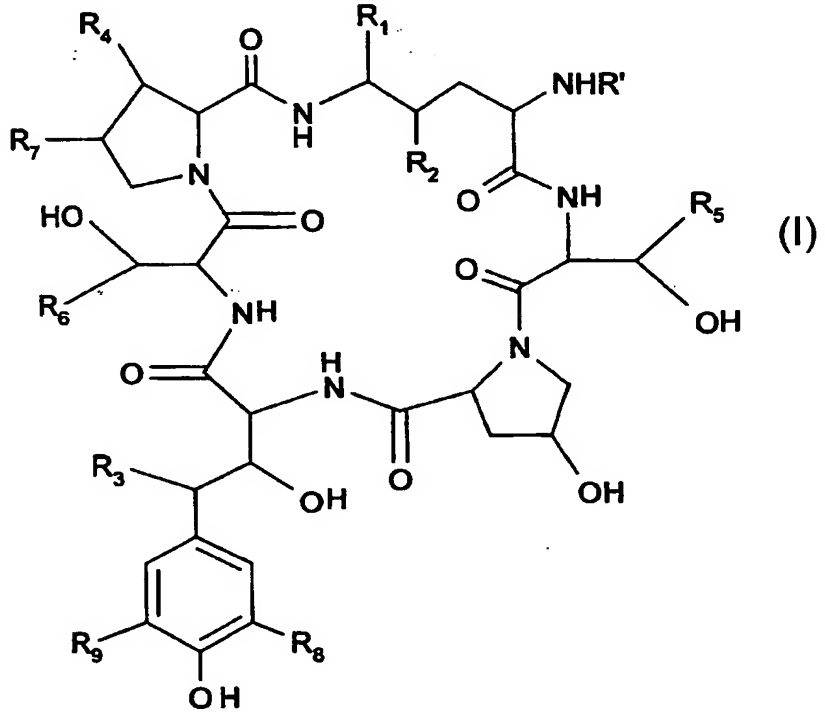
(74) Agent: VIEILLEFOSSE, Jean-Claude; Hoechst Marion Roussel, 102, route de Noisy, F-93235 Romainville Cedex (FR).

(81) Designated States *(national)*: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian

[Continued on next page]

(54) Title: NOVEL CYCLOHEXAPEPTIDE COMPOUNDS, PROCESSES FOR THEIR PRODUCTION AND THEIR USE AS A PHARMACEUTICAL



(I)

(57) Abstract: A cyclohexapeptide compound of general formula (I), wherein R^1 is C_1-C_{20} alkyl; C_9-C_{20} alkenyl; C_9-C_{20} alkoxyphenyl; an aryl group selected from: phenyl, biphenyl, terphenyl and naphthyl; C_1-C_{12} alkylphenyl, C_2-C_{12} alkenylphenyl, C_1-C_{12} alkoxyphenyl; linoleoyl; palmitoyl; 12-methylmyristoyl; 10,12-dimethylmyristoyl; or $-COC_6H_4(p)OC_8H_{17}$, R_1 and R_3 are independently -OH; -CN; $-CH_2NH_2$; $-N_3$; aryl; substituted aryl; heterocyclyl and substituted heterocyclic with 1-3 of the same or different heteroatoms; aminoalkylamino; mono or di-substituted linear or cyclic aminoalkylamino; -OR, wherein, R is C_1-C_{12} alkyl; substituted alkyl of the type $-(CH_2)_n$-X, where n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2 or a heterocyclic and where Y is C_1-C_6 linear or branched alkyl; C_2-C_{12}-alkenyl; aryl; fused aryl; substituted aryl; a heterocyclic containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group; and R_3 may additionally be imidazolyl; R_2 and R_4 are independently -H or -OH; R_5 is -H or $-CH_3$. R_6 is -H, $-CH_3$ or $-CH_2CONH_2$. R_7 is -H, $-CH_3$ or -OH. R_8 and R_9 are independently -H or $-CH_2$-Sec.amine in which the sec.amine is attached to $-CH_2$ through its N linkage; and its pharmaceutically acceptable salts. The compounds are useful as antifungal agents.

WO 01/07468 A2

patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

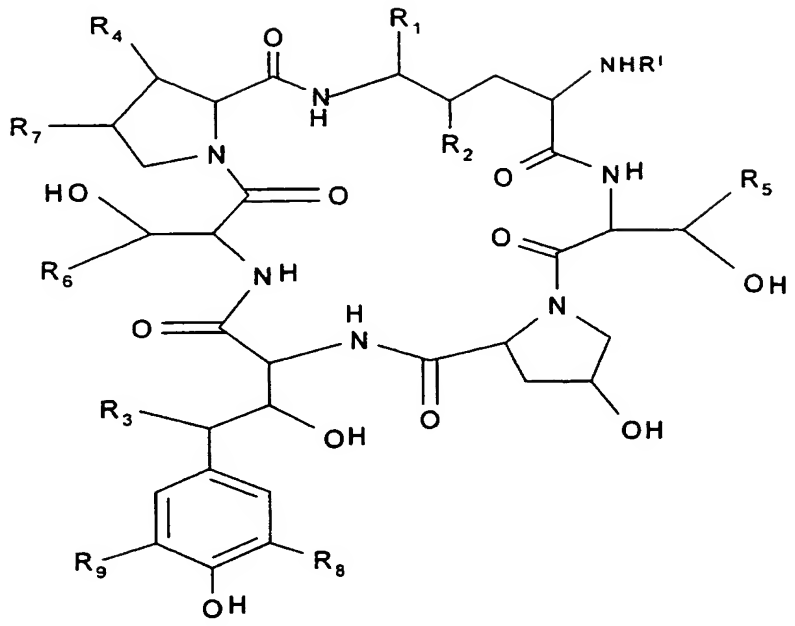
NOVEL CYCLOHEXAPEPTIDE COMPOUNDS, PROCESSES FOR THEIR PRODUCTION AND THEIR USE AS A PHARMACEUTICAL

Novel cyclohexapeptide compounds, processes for their production and their use as a pharmaceutical.

The present invention relates to cyclohexapeptide compounds belonging to the echinocandin class having a substituent group at the ornithine-5, homotyrosine-4 and ortho position of the phenolic hydroxy of the homotyrosine unit, and pharmaceutically acceptable salts thereof. The present invention further relates to processes for the preparation of the novel cyclohexapeptide compounds, to the use of the compounds and their pharmaceutically acceptable salts as pharmaceuticals, in particular to their use in the treatment of fungal infections, and to pharmaceutical compositions comprising the novel compounds or a pharmaceutically acceptable salt thereof.

The search for new and effective antifungal agents has been intensified by the increase in immunological diseases and aggressive immunosuppressive chemotherapy. Present therapeutic options for the treatment of fungal infections are limited to compounds in two classes, the polyenes and the azoles. Due to an increase in the number of isolates, which are resistant to conventional antifungal agents, there presently exists a need for new antifungal and anti-pneumocystis agents. Because there are limited numbers of antifungal agents available for the treatment of life-threatening fungal infections and because resistance may further limit the utility of the newer azoles, there is an urgent need for new antifungal agents with a different mode of action.

Accordingly, the present invention provides novel antifungal cyclohexapeptide compounds represented by general formula I as shown below:



I

wherein

R^I is C_9-C_{20} alkyl; C_9-C_{20} alkenyl; C_9-C_{20} alkoxyphenyl; an aryl group selected from: phenyl, biphenyl, terphenyl and naphthyl; C_1-C_{12} alkylphenyl, C_2-C_{12} alkenylphenyl, C_1-C_{12} alkoxyphenyl; linoleoyl; palmitoyl; 12-methylmyristoyl; 10,12-dimethylmyristoyl; or $-COC_6H_4(p)OC_8H_{17}$;

R_1 and R_3 are independently -H; -OH; -CN; $-CH_2NH_2$; $-N_3$; aryl; substituted aryl; heterocyclyl and substituted heterocyclyl with 1-3 of the same or different heteroatoms; aminoalkylamino; mono or di-substituted linear or cyclic aminoalkylamino; -OR, wherein, R is C_1-C_{12} alkyl; substituted alkyl of the type $-(CH_2)_n$-X ,where n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2 or a heterocyclic and where Y = C_1-C_6 linear or branched alkyl; C_2-C_{12}-alkenyl; aryl; fused aryl; substituted aryl; a heterocyclic containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group; or R_3 is imidazolyl;

R_2 and R_4 are independently -H or –OH;

R_5 is -H or $-CH_3$;

R_6 is -H, $-CH_3$ or $-CH_2CONH_2$;

R_7 is -H, $-CH_3$ or –OH;

R_8 and R_9 are independently -H or -CH_2-Secondary amine, the secondary amine being attached to –CH_2 through its N-linkage; and its pharmaceutically acceptable salts.

To the nitrogen atom of the secondary amine are attached the same or different groups selected from: C_1-C_{12} alkyl, C_2-C_{12} alkenyl, aryl, substituted aryl, alkylaryl and substituted alkylaryl, or the nitrogen atom of the secondary amine is part of a heterocyclic group, optionally substituted by one or more of: C_1-C_6 alkyl, C_2-C_6 alkenyl, aryl, amino, nitro and halogen, or a fused heterocyclic group, whereby the heterocyclic group in each case contains 1-3 of the same or different heteroatoms.

Examples of suitable secondary amines are piperidine, pyrrolidine, 4-methyl-piperidine, morpholine, dimethylamine, diisopropylamie, 4-piperidino-piperidine, piperazine, 1-methylpiperazine, 1-(2-fluorophenyl)piperazine, 1-(2-chlorophenyl)piperazine, 1-(2-pyrimidyl)piperazine, 1-(4-fluorophenyl)piperazine, N-(α,α,α-trifluoro-m-tolyl)piperazine, 1-phenylpiperazine, 1-benzylpiperazine, 1-(2-pyridyl)piperazine, 1-(4-pyridyl)piperazine, 1-(4-methylphenyl) piperazine, 1-(2,6-dimethylphenyl)piperazine, 1-(1-phenylethyl)piperazine, dibenzylamine, N-(tert-butyl)benzylamine, and N-(isopropyl)benzylamine.

In a preferred first embodiment, R_1 is -OH or -OR and R_3 is -OH, -OR or imidazolyl, wherein R in each case is C_1-C_{12} alkyl, substituted alkyl of the type -$(CH_2)_n$-X, where n is 1-5, X is Cl, Br, I, COOY, CN, NH_2 or a heterocyclic and Y is a C_1-C_6 linear or branched alkyl; C_2-C_{12}-alkenyl; aryl; fused aryl; substituted aryl; a heterocyclic containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group.

Ideally in the first embodiment R_8 and /or R_9 is –CH_2-secondary amine.

In an alternative preferred embodiment R^1 is 12-methylmyristoyl, R_1 and R_3 are independently -OH, -CN, -CH_2NH_2, -N_3, aryl, substituted aryl, a heterocyclyl or a substituted heterocyclyl, having the heterocyclyl in each case 1-3 of the same or different heteroatoms, aminoalkylamino, or mono or di-substituted linear or cyclic

aminoalkylamino, R_2 and R_4 are both –OH, R_5 and R_7 are both $-CH_3$, R_6 is –H, and R_8 and R_9 are both –H.

The compounds provided by this invention are semi-synthetic cyclic hexapeptides derived from cyclic peptides, which are produced by culturing various microorganisms. A number of cyclic peptides are known in the literature, including mulundocandin, sporiofungin, echinocandin B and aculeacin.

These cyclic hexapeptides have closely related structures with some modification of the cyclic peptide and / or the N-acyl fatty acid chain. For example mulundocandin has a methyl-myristoyl side chain, aculeacin A has a palmitoyl side chain, echinocandin B has a linoleoyl side chain and pneumocandin Ao has a di-methylmyristoyl side chain. The naturally occurring cyclic hexapeptides of the echinocandin class have a labile C-O bond and C-N bond at the ornithine-5 position as disclosed in US-A-5,378,804 issued January 3, 1995.

According to the present invention there are further provided processes for the preparation of novel cyclohexapeptide compounds of general formula I above.

The invention is described herein using the terms defined below unless otherwise specified.

Throughout the specification and appended claims, a given chemical formula or name shall encompass all optical and stereoisomers as well as racemic mixtures where such isomers and mixtures exist.

As used herein, the term "C_1-C_{12} alkyl" refers to a straight or branched alkyl chain having from one to twelve carbon atoms. Typical C_1-C_{12} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. The term "C_1-C_{12} alkyl" includes within its definition the term "C_1-C_6 alkyl".

The term "C_9-C_{20} alkyl" refers to a straight or branched alkyl chain having from nine to twenty carbon atoms.

The term "C_1-C_{12} alkenyl" refers to a straight or branched chain hydrocarbon having from one to twelve carbon atoms, with at least one unsaturation. Typical alkenyl groups are groups such as vinyl, 1-propen-2-yl, 1-buten-4-yl, 2-buten-4-yl and 1-penten-5-yl.

The term "C_9-C_{20} alkenyl" refers to a straight or branched alkyl chain having from nine to twenty carbon atoms with at least one saturation.

The term "C_9-C_{20} alkoxy" refers to a straight or branched alkyl chain having from nine to twenty carbon atoms attached to an oxygen atom. Typical C_9-C_{20} alkoxy groups are, for example, decyloxy, and dodecyloxy.

The term "substituted alkyl" refers to alkyl groups which may be substituted with up to three substituent groups at any available point of attachment.

The term "cycloalkyl" refers to a species of alkyl containing from 3 to 15 carbon atoms without altering or resonating double bonds between carbon atoms.

The term "aryl" refers to, for example, a phenyl which is optionally substituted by one or more substituents such as halogen, alkyl, alkoxy or nitro.

The term "fused aryl" refers to a bicyclic or polycyclic ring system such as benzene ring having any two adjacent carbon atoms in common. Typical examples of fused aryl groups are naphthalene and anthracene.

The term "heteroatom" refers to N, O, S, and P.

The term "heterocyclic" refers to a 3, 5, 6 or 7 membered ring having 1 to 3 hetero atoms which may be nitrogen, oxygen or sulphur, including pyrrolyl, pyrrolidinyl, pyridonyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, isoxazolyl, furyl, thienyl, oxazolyl, thiazolyl, piperidyl, morphinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, imidazolidinyl and piperazinyl.

The term "hydroxyprotecting group" refers to a substituent of an hydroxy group that is commonly employed to block or protect the hydroxy functionality while reactions are carried out on the other functional groups on the compound. Examples of such hydroxy protecting groups include tetrahydropyranyl, methoxymethyl, methylthiomethyl, t-butyl, t-amyl, trityl, benzyl, allyl, trimethylsillyl and (t-butyl)dimethylsilyl. The species of hydroxy protecting group is not critical so long as the derivatized hydroxy group is stable to the conditions of the subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. Preferred hydroxy protecting groups are benzyl and methyl. The term "protected hydroxy" refers to a hydroxy group bonded to one of the above hydroxy protecting groups.

Further examples of hydroxy protecting groups are described in T. W. Greene, "Protective Groups in Organic Synthesis" John Wiley and Sons, New York, N. Y. (2nd edition, 1991) Chapters 2 and 3.

One process for the preparation of cyclohexapeptide compounds of the general formula I above according to the present invention comprises:

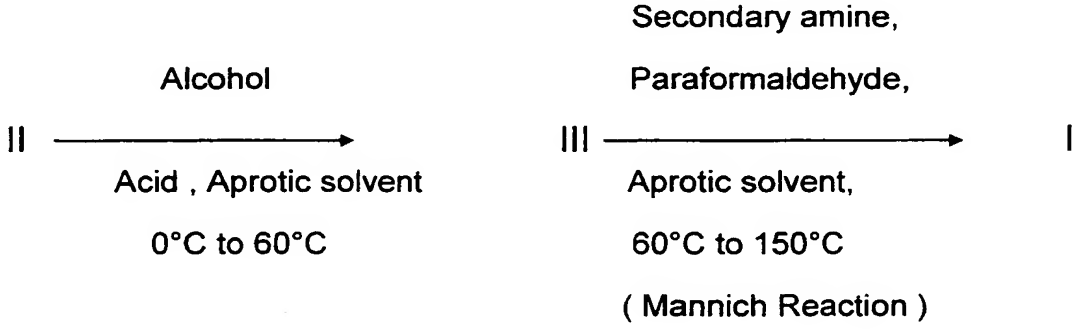
a) reacting a cyclohexapeptide compound of the general formula I above, wherein R^1, R_2, R_4, R_5, R_6 and R_7 are as defined above in the general formula I, R_1 and R_3 are both –OH, and R_8 and R_9 are -H (compound II), with an alcohol in the presence of an acid in an aprotic solvent, at a temperature ranging from 0°C to 60° to obtain the corresponding cyclohexapeptide derivative of the formula I wherein R^1, R_2, R_4, R_5, R_6 and R_7 are as defined in the general formula I, R_1 and R_3 are –OH or –OR, such that at least one of R_1 or R_3 is –OR, wherein R is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, fused aryl, substituted aryl, a heterocyclyl containing 1-3 heteroatoms, mono or di-substituted aminoalkyl, or a hydroxy protecting group, and R_8 and R_9 are –H (compound III);

b) reacting the compound III obtained in step (a) with an appropriate secondary amine in the presence of paraformaldehyde in an aprotic solvent at a temperature ranging from 60°C to 150°C to yield the desired compound of

formula I, isolating and purifying the resulting compound of formula I from the reaction mixture in a known manner and if desired, converting the compound of formula I into its pharmaceutically acceptable salt in a known manner.

The final compounds of formula I can be purified by procedure well known in the art such as crystallization followed by filtration. Alternatively the solvent can be removed by extraction, evaporation and the intermediates can be purified if required by chromatography with solid support such as silica gel, alumina, RP-8 or RP-18.

The described process for the preparation of the cyclohexapeptide compound of general formula I is illustrated as follows:



SCHEME 1

The reaction of step (b) wherein the intermediate compounds III are reacted with a secondary amine in the presence of paraformaldehyde is known in the art as a Mannich Reaction.

The starting compounds II may be natural products such as mulundocandin, echinocandin B, aculeacin, pneumocandin Ao , pneumocandin Bo, pneumocandin Co and cilofungin.

In the process of the present invention, the alcohol used in step (a) may be an alkyl alcohol such as methanol or an aryl alcohol such as benzyl alcohol.

For step (a), suitable acids include strong organic acid such as trifluoroacetic acid, p-toluene sulphonic acid, camphor sulphonic acid or a lewis acid such as borontrifluoride etherate, titanium tetrachloride.

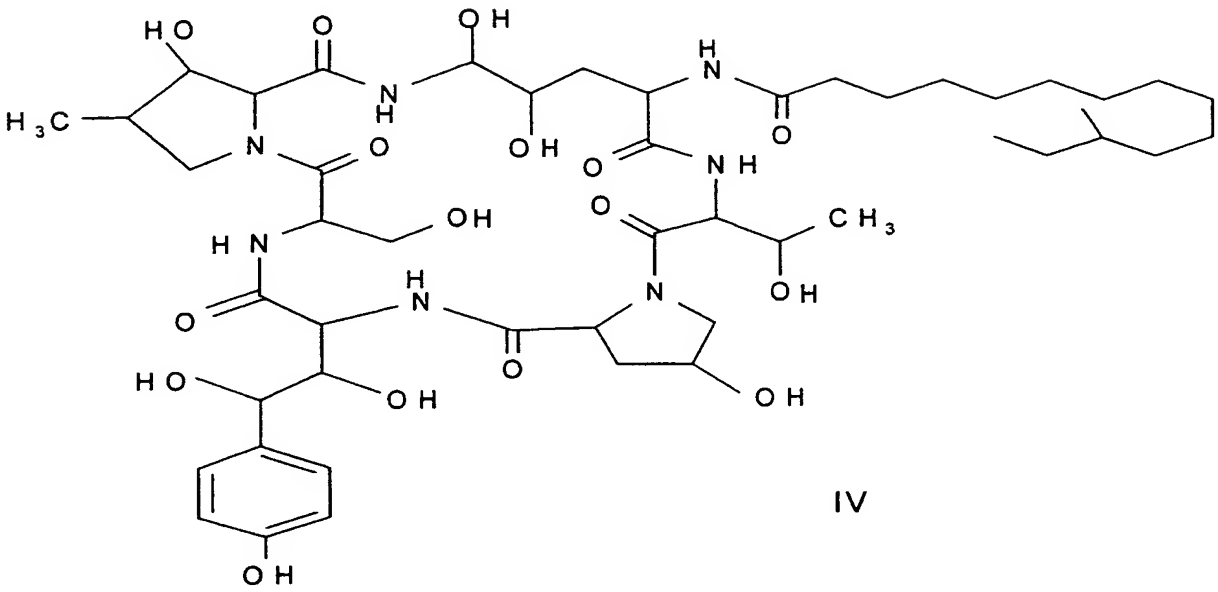
Suitable aprotic solvents used in steps (a) and (b) are selected from 1,4-dioxane, N,N-dimethylformamide(DMF), dimethylsulfoxide(DMSO), tetrahydrofuran(THF), toluene. The preferred one is 1,4-dioxane.

In step (b), the said secondary amines include compounds in which the nitrogen contains the same or different C_1-C_{12} alkyl, C_2-C_{12} alkenyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl groups, and compounds in which the nitrogen atom of the secondary amine may be a part of a heterocyclic or substituted heterocyclic or fused heterocyclic. The heterocyclics may contain 1-3 of the same or different heteroatoms. Substituted heterocyclics may contain substituent(s) such as C_1-C_6 alkyl, C_1-C_6 alkenyl, aryl, amino, nitro and/or halogens.

Some representative examples of secondary amines are listed below: piperidine, pyrrolidine, 4-methylpiperidine, morpholine, dimethylamine, diisopropylamie, 4-piperidino-piperidine, piperazine, 1-methylpiperazine, 1-(2-fluorophenyl)piperazine, 1-(2-chlorophenyl)piperazine, 1-(2-pyrimidyl)piperazine, 1-(4-fluorophenyl)piperazine, N-(α,α,α-trifluoro-m-tolyl)piperazine, 1-phenylpiperazine, 1-benzylpiperazine, 1-(2-pyridyl)piperazine, 1-(4-pyridyl)piperazine, 1-(4-methylphenyl) piperazine, 1-(2,6-dimethylphenyl)piperazine, 1-(1-phenylethyl)piperazine, dibenzylamine, N-(tert-butyl)benzylamine and N-(isopropyl)benzylamine.

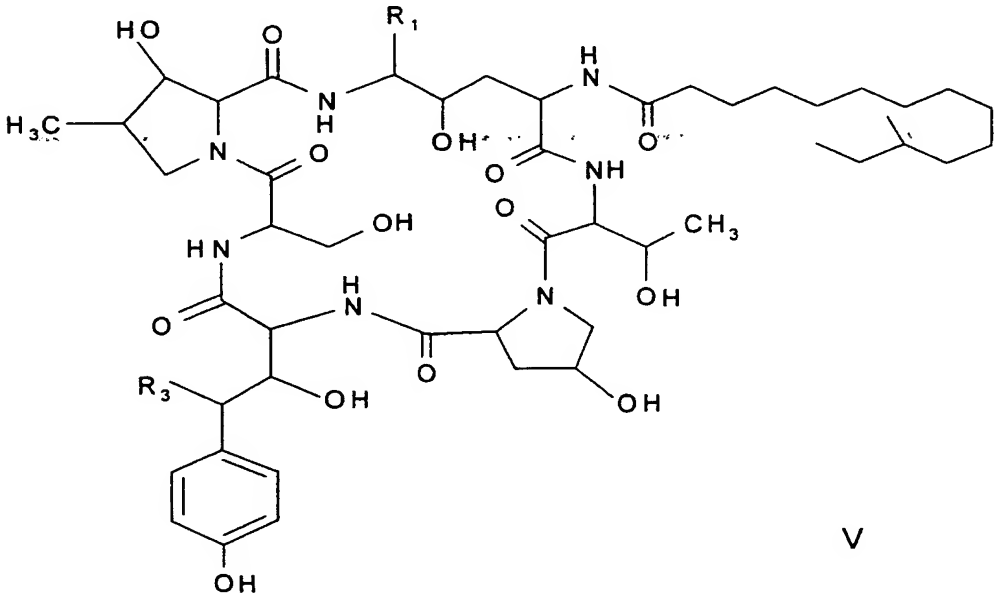
The present invention provides a second process for the preparation of compounds of the general formula I comprising:

a) reacting mulundocandin of the following formula IV,



IV

with a nucleophile such as a thiol or a thioether in presence of an acid in an aprotic solvent at a temperature ranging from 0°C to 60° to obtain the corresponding cyclohexapeptide derivatives of formula V;



V

wherein R_1 and R_3 are independently –OH or –SR such that at least one of R_1 or R_3 is –SR, wherein R is C_1-C_{12} alkyl, substituted alkyl of the type -$(CH_2)_n$-X, wherein n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2, or a heterocyclic and Y is a C_1-C_6 linear or branched alkyl; C_2-C_{12} alkenyl; aryl; fused aryl; substituted aryl; heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group ;

b) reacting the compounds of formula V as obtained in step (a) with an oxidising agent in an aqueous medium at a temperature ranging from 20°C to 60°C to obtain the corresponding sulfones of the formula VI, wherein in formula V above R_1 and R_3 are independently –OH or -S (O_2)R, such that at least one of R_1 or R_3 is $-SO_2R$, wherein R is a C_1-C_{12} alkyl, substituted alkyl of the type -$(CH_2)_n$-X, wherein n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2, a heterocyclic, Y is a C_1-C_6 linear or branched alkyl chain; C_2-C_{12} alkenyl; aryl; fused aryl; substituted aryl; heteroaryl containing 1-3 heteroatoms; heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group;

c) reacting the sulfone (VI) obtained in step (b) with an appropriate nucleophile such as a carbon or nitrogen nucleophile in an appropriate solvent at a temperature ranging from 20°C to 60°C to obtain the desired compound of the formula I, isolating and purifying the resulting compound of the formula I from the reaction mixture in a known matter and, if desired, converting the compound of formula I into its pharmaceutically acceptable salt in a known manner

The final compound of formula I can be purified by procedure well known in the art such as crystallisation followed by filtration. Alternatively the solvent can be removed by extraction, evaporation and the intermediate can be purified if required by chromatography with solid support such as silica gel, alumina, RP-8 or RP-18.

The process for the preparation of the cyclohexapeptide compounds of general formula I is illustrated as follows:

thiother or thiol,	oxidising agent,	Nucleophile,
IV ⟶	V ⟶	VI ⟶ I
acid, aprotic solvent	aqueous medium	aprotic solvent
0°C to 60°C	20°C to 60°C	20°C to 60°C

SCHEME 2

The starting, compound, Mulundocandin, is a naturally occurring cyclic lipopeptide, which is isolated from the cultured broth of a strain of Aspergillus sydowi, a microorganism (Indian Patent No. 162032; The Journal of Antibiotics, Vol. XL No. 3, 275-277). Mulundocandin is useful as an antibiotic.

In the process of the present invention the said nucleophile used in step (a) may be a thioether such as methylthioglycolate or an aryl thiol such as thiophenol.

Step (a) is carried out in presence of an acid which may be a strong organic acid such as trifluoroacetic acid, p-toluene sulphonic acid, camphor sulphonic acid or a lewis acid such as boron trifluoride etherate, titanium tetrachloride.

Suitable aprotic solvents used in steps (a) and (c) are selected from 1,4-dioxane, N, N-dimethylformamide(DMF), dimethylsulfoxide(DMSO), tetrahydrofuran(THF) and toluene. The preferred one is 1, 4-dioxane.

In step (b), the suitable oxidising agent includes OXONE® ($KHSO_5.KHSO_4.K_2SO4$:: 2:1:1; obtained from Aldrich Chemicals), hydrogen peroxide and metachloroperbenzoic acid. The preferrred one is OXONE®.

The said aqueous medium used in the oxidation step is usually a mixture of solvents consisting of water and a water soluble organic solvent such as acetonitrile, dimethylformamide, dimethylsulfoxide and tetrahydrofuran. About 1:1 v/v mixture of the solvents is preferred. The preferred water soluble organic solvent is acetonitrile.

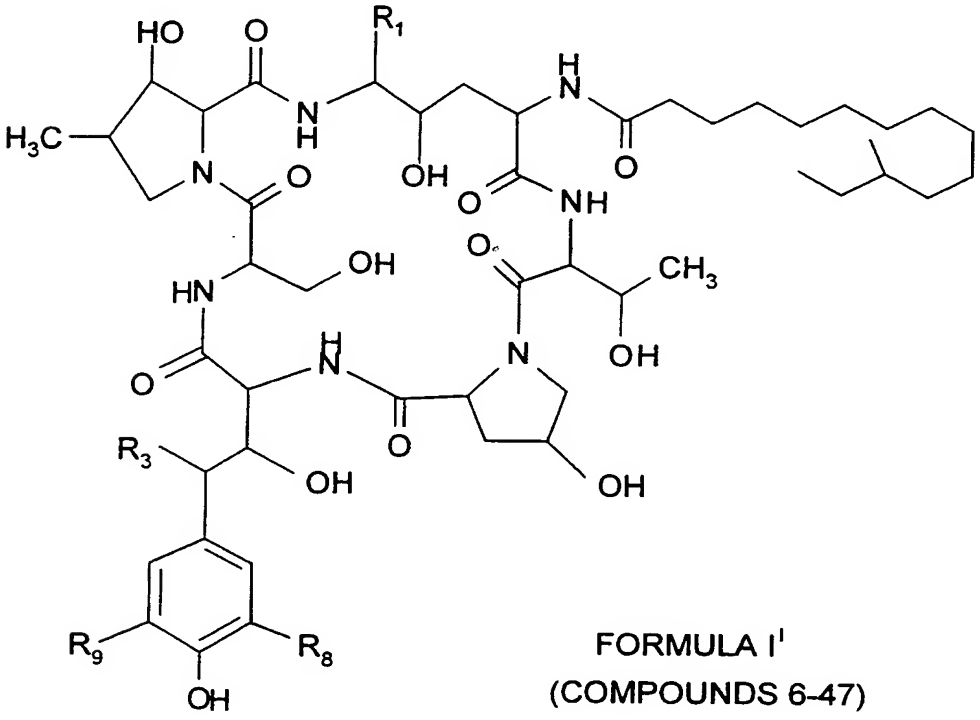
In step (c), the said nucleophile includes a carbon nucleophile or a nitrogen nucleophile.

The carbon nucleophile may be a cyanide such as sodium cyanide, potassium cyanide and lithium cyanide.

The nitrogen nucleophile may be selected from an amine, azide, heterocyclyl, substituted heterocyclyl (containing 1-3 of the same or different heteroatoms), and aminoalkylamino compounds.

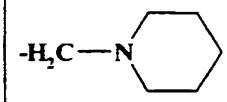
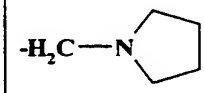
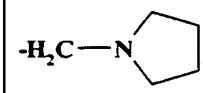
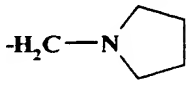
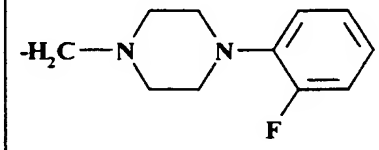
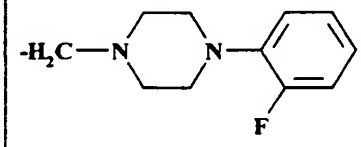
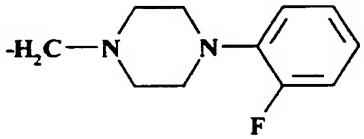
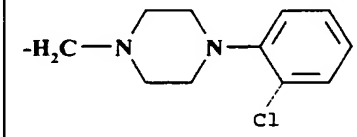
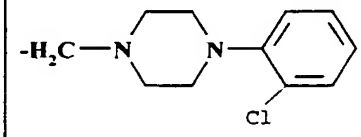
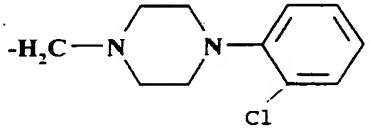
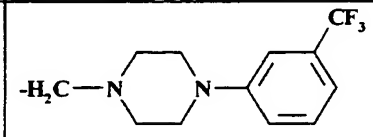
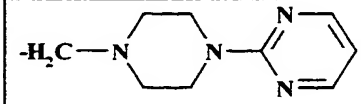
In the second process of the present invention the nucleophilic substitution may take place either at ornithine-5 position only or at both the ornithine-5 and homotyrosine-4 positions depending on the intermediates formed in step (a).

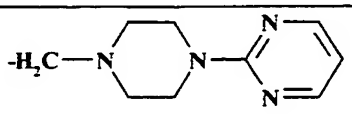
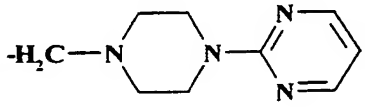
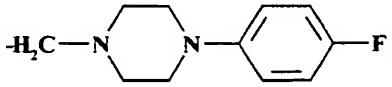
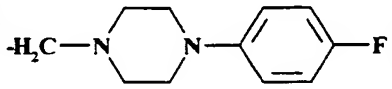
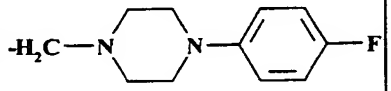
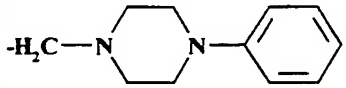
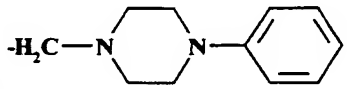
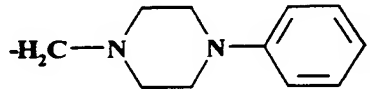
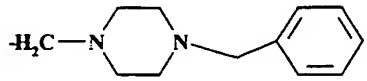
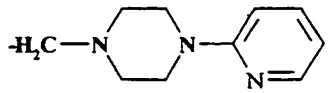
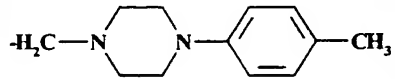
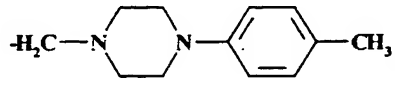
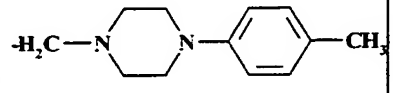
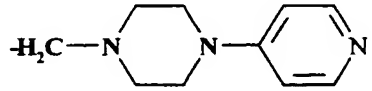
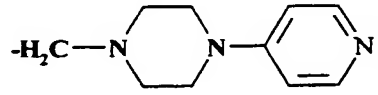
The preferred representatives of cyclohexapeptide compounds of formula I' below are listed in the following Table I.

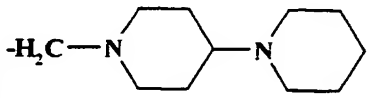
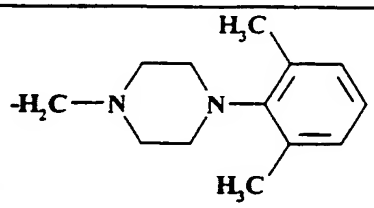
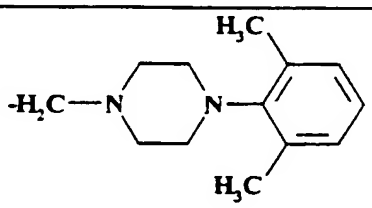
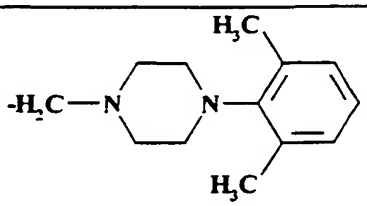
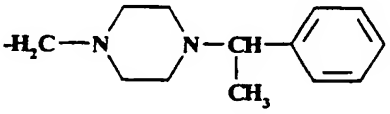
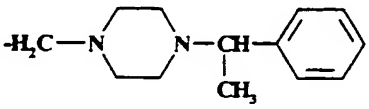
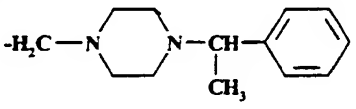
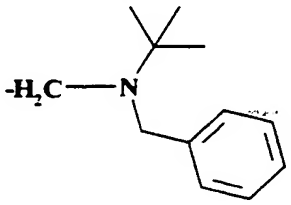
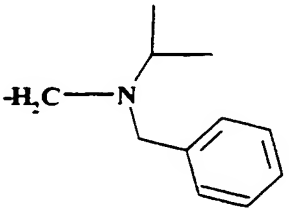


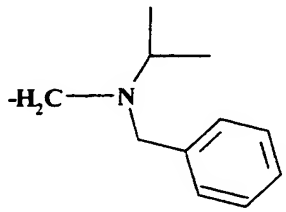
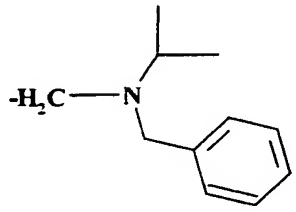
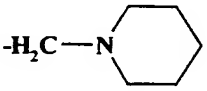
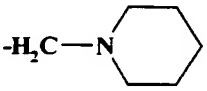
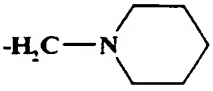
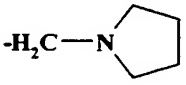
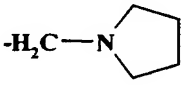
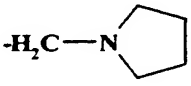
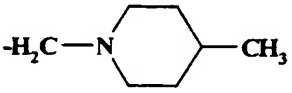
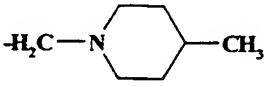
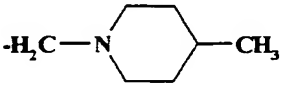
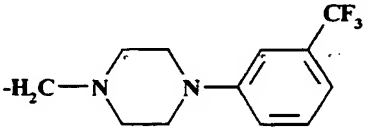
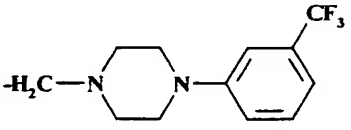
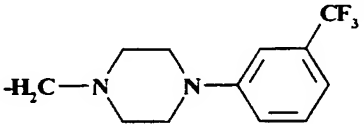
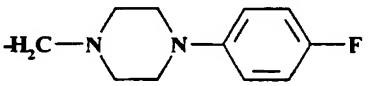
FORMULA I'
(COMPOUNDS 6-47)

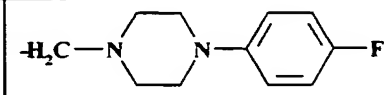
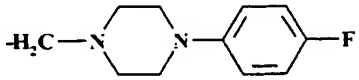
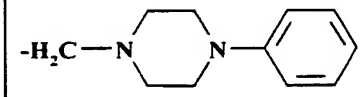
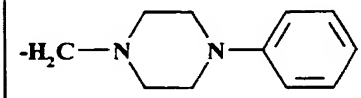
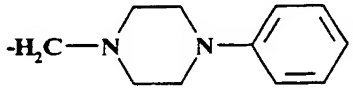
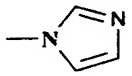
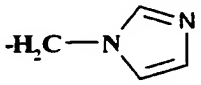
TABLE I

COMPD NO	R_1	R_3	R_8	R_9
6	$-OCH_2Ph$	-OH		-H
7	$-OCH_2Ph$	-OH		-H
8	$-OCH_2Ph$	-OH		
9	$-OCH_2Ph$	-OH		-H
10	$-OCH_2Ph$	-OH		
11	$-OCH_2Ph$	-OH		-H
12	$-OCH_2Ph$	-OH		
13	$-OCH_2Ph$	-OH		-H
14	$-OCH_2Ph$	-OH		-H

COMPD NO	R_1	R_3	R_8	R_9
15	$-OCH_2Ph$	-OH		
16	$-OCH_2Ph$	-OH		-H
17	$-OCH_2Ph$	-OH		
18	$-OCH_2Ph$	-OH		-H
19	$-OCH_2Ph$	-OH		
20	$-OCH_2Ph$	-OH	$-CH_2N(CH_2Ph)_2$	-H
21	$-OCH_2Ph$	-OH		-H
22	$-OCH_2Ph$	-OH		-H
23	$-OCH_2Ph$	-OH		-H
24	$-OCH_2Ph$	-OH		
25	$-OCH_2Ph$	-OH		

COMPD NO	R_1	R_3	R_8	R_9
26	$-OCH_2Ph$	-OH		-H
27	$-OCH_2Ph$	-OH		-H
28	$-OCH_2Ph$	-OH		
29	$-OCH_2Ph$	-OH		-H
30	$-OCH_2Ph$	-OH		
31	$-OCH_2Ph$	-OH		-H
32	$-OCH_2Ph$	-OH		-H

COMPD NO	R_1	R_3	R_8	R_9
33	$-OCH_2Ph$	-OH		
34	$-OCH_2Ph$	$-OCH_2Ph$		-H
35	$-OCH_2Ph$	$-OCH_2Ph$		
36	$-OCH_2Ph$	$-OCH_2Ph$		-H
37	$-OCH_2Ph$	$-OCH_2Ph$		
38	$-OCH_2Ph$	$-OCH_2Ph$		-H
39	$-OCH_2Ph$	$-OCH_2Ph$		
40	$-OCH_2Ph$	$-OCH_2Ph$		-H
41	$-OCH_2Ph$	$-OCH_2Ph$		
42	$-OCH_2Ph$	$-OCH_2Ph$	$-CH_2N(CH_2Ph)_2$	-H
43	$-OCH_3$	-OH		-H

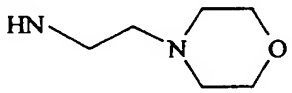
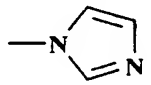
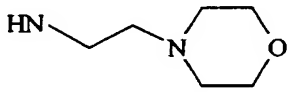
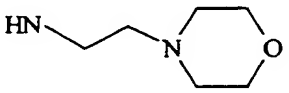
COMPD NO	R_1	R_3	R_8	R_9
44	$-OCH_3$	-OH		
45	$-OCH_3$	-OH		-H
46	$-OCH_3$	-OH		
47	$-OCH_2OH$			H

The compounds (6-47) listed in the Table 1 are prepared from Mulundocandin (Formula IV above, compound 1) as the starting material whereby in the general formula I R^1 is 12-methylmyristoyl; R_1, R_2, R_3 and R_4 each represent -OH, R_5 and R_7 each represents $-CH_3$, R_6 represents –H and R_8 and R_9 are -H.

The preferred representatives of intermediate compounds III are compounds 2-5 as described in the experimental section of the specification.

The further preferred representative compounds given in Table II have the general formula I' above in which R^8 and R^9 are H and R_1 and R_3 are the groups shown in the Table.

TABLE II

COMPD NO	R_1	R_3
54	CN	-OH
55	CH_2NH_2	-OH
56		-OH
57		-OH
58	CN	CN
59	N_3	N_3
60		

The preferred representatives of intermediate compounds of general formula V and VI are compounds 49-53 as described in the experimental section of the specification.

The compound 55 as shown in Table II is obtained by reduction of compound 54 with a reducing agent such as $CoCl_2$-$NaBH_4$ or by hydrogenation using raney nickel as a catalyst in presence of ammonia in alcoholic solvent.

The compounds of general formula I, if desired may be converted into their pharmaceutically acceptable salts.

Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acid such as hydrochloric acid and those formed with organic acid such as acetic acid.

The compounds of present invention are soluble in lower alcohols and polar aprotic solvents such as N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and pyridine.

The compounds of present invention are useful for the control of both filamentous fungi and yeast. They are especially adaptable to be employed for the treatment of mycotic infections in mammals, especially those caused by Candida species such as C.albicans, C.tropicals and C.neoforma and Aspergillus species such as A.fumigatus, A.flavus and A.niger. These type of infections are usually found in immunocompromised patients such as those suffering from AIDS.

The compounds of formula I of the present invention and pharmaceutically acceptable salts thereof may be administered orally, intramuscularly, intravenously or by other modes of administration. Pharmaceutical compositions which contain the compound according to the invention or a pharmaceutically acceptable salt or derivative thereof singly or in combinations can be prepared according to standard techniques by mixing the compound(s) with one or more pharmacologically acceptable excipients and/or auxiliaries such as fillers, emulsifiers, lubricants, masking flavours colorants or buffer substances, and converting the mixture into a suitable pharmaceutical form such as tablets, coated tablets, capsules or a suspension or solution suitable for enteral or parental administration. Further details of the production of suitable pharmaceuticals may be obtained from the literature which relates to the echinocandin type of antibiotics.

As cusomary, the galenic formulation and the method of administration as well as the dosage range which are suitable in a specific case depend on the species to be treated and on the state of the respective condition or disease, and can be optimized using methods known in the art. On an average, the daily dose of a compound of the formula I in a patient of about 75 kg weight is at least 0.001 mg to at most 10 mg, preferably at most 1.0 mg.
The compounds disclosed herein have basic amino-functionality at the ornithine/homotyrosine unit(s), imparting solubility of compounds through their salts.

The following examples illustrate the invention but are not to be considered as limiting the scope of the invention.

The terms infrared spectra, electron spray ionization mass spectra, proton nuclear magnetic resonance spectra, ^{13}C-nuclear magnetic resonance spectra, melting point, ultraviolet spectra, thin layer chromatography, high pressure liquid chromatography are abbreviated "IR", "ESI MS", "^{1}H NMR", "^{13}C NMR", "m.p.", "UV", "TLC", "HPLC" respectively.

In conjunction with the ^{1}H NMR spectra, the following abbreviations are used : "s" is singlet, "d" is doublet, "t" is triplet, "q" is quartet, "dd" is doublet of doublet, "br" is broad, "br.s" is broad singlet, "br.d" is broad doublet, "br.t" is broad triplet, "br.m" is broad multiplet, "J" indicates the coupling constant in Hertz (hz). ^{1}H NMR, ^{13}C NMR, IR, MS, HPLC, m.p. data refers to the free base of the subject compound, unless otherwise mentioned.

Melting points were recorded on a Kofler hot-plate apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 157 spectrophotometer using KBr pellets. ^{1}H NMR were recorded on a Brucker ACP-300 MHz instrument using CD_3OD as solvent, unless otherwise mentioned. The chemical shifts are expressed in delta (δ) values (parts per million downfield from tetramethylsilane). ^{13}C NMR were recorded on a Brucker ACP-300 and the chemical shifts are expressed in ppm. Electron spray ionization mass spectra (ESI MS) were recorded on a VG QUATTRO II instrument. Perkin Elmer 235 HPLC were used for purification (Semipreparative column- Knauer Eurosphere 100, C-18 column, 250 x 16 mm, 10 μm, λ = 220 & 270 nm) and for checking purity (Analytical column -YMC-Pack, AQ-313 S-5 120A ODS, C-18 column, 6 x 250 mm, 5 μm, λ = 220 & 270 nm) of the compounds, according to the invention.

Procedure for the preparation of compounds 2 & 3 :-

To a stirred solution of mulundocandin 1 (5.2 g, 5.15 mmol) in anhydrous 1,4-dioxane (150 ml), under nitrogen atmosphere was added anhydrous benzyl alcohol

(10.45 g, 96.6 mmol), and a catalytic amount of p-toluenesulfonic acid (0.32 g, 1.66 mmol) and the resulting reaction mixture was stirred at ambient temperature for 1 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). TLC analysis after 1 hr. showed no starting compound. The reaction was quenched at 5-10 °C by the addition of saturated aqueous $NaHCO_3$ and evaporated to smaller volume (25 ml). The above mixture was diluted with water (250 ml), extracted with n-butanol(3 x 150 ml) and washed with water (200 ml) followed by brine (200 ml). Combined organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give crude gummy product, which was then dissolved in a minimum amount of methanol(15 ml), adsorbed on silica gel (1:1 w/w), and was subjected to silica gel flash column chromatography. 0-15 % MeOH/$CHCl_3$ was used as 5 % step gradient elution. Evaporation of the appropriate fractions gave white compound 2 (3.8 g, 67.13 %) and 3 (0.82 g, 13.37 %).

Compound 2 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-1-hydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxy-ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxo-perhydrodiazolo[2,1-c:2,1-*f*][1,4,7, 10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^1H NMR : 7.28 – 7.41 (m, 5H, OCH_2Ph), 7.17 (d, 2H, 8.37 Hz., Ar-H), 6.78 (d, 2H, 8.37 hz., Ar-H), 4.68 (s, 2H, OCH_2Ph)

^{13}C NMR spectrum of ornithine5-benzylmulundocandin (in DMSO-d_6) :

172.07, 171.51, 170.46, 170.27, 169.59, 168.14, 156.57, 138.78, 132.47, 128.19, 127.94, 127.35, 127.08, 114.65, 79.01, 75.19, 74.24, 73.19, 69.23, 68.99, 68.66, 68.04, 66.10, 62.27, 60.82, 56.29, 55.67, 53.49, 51.84, 51.28, 49.23, 37.26, 36.99, 35.99, 35.13, 34.72, 33.73, 29.36, 29.03, 28.90, 28.52, 26.45, 25.42, 19.38, 19.06, 11.19, 10.81.

IR(KBr): 3350-3450 br, 2930, 1650 br, 1615, 1520, 1450, 1385(sharp), 1220, 1070 cm^{-1}.

ESI MS(ES+): for $C_{55}H_{83}N_7O_{16}$

Calculated : 1098.292

Found : $(M+Na)^+$ = 1120.7 (base peak), 567.4.

UV(MeOH): λ_{max} : 206, 225, 277 nm (ε = 31040, 14016, 1595)

Compound 3 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-1-hydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxy-ethyl)-20-hydroxy-methyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexa-azacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.24 – 7.31 (m, 5H, 2 x OCH_2Ph), 7.12 (d, 2H, 8.55 Hz., Ar-H), 6.74 (d, 2H, 8.55 hz., Ar-H), 4.4 – 4.53 (2 x s, 4H, 2 x OCH_2Ph)

IR(KBr):-3350-3450 br, 2930, 1650 br, 1615, 1520, 1450, 1385(sharp), 1220, 1070 cm^{-1}.

ESI MS(ES+): for $C_{62}H_{89}N_7O_{16}$

Calculated : 1188.416

Found : $(M+Na)^+$ = 1210.3(base peak), 1146.2, 567.4.

UV(MeOH) : λ_{max} : 209, 228, 275 nm (ε = 30025, 14113, 1767)

Procedure for the preparation of compounds 4 & 5 :-

To a stirred solution of mulundocandin 1 (2.2 g, 2.18 mmol) in anhydrous 1,4-dioxane (50 ml), under nitrogen atmosphere was added anhydrous methanol(6.0 ml, 147.9 mmol), and a catalytic amount of p-toluenesulfonic acid (0.12 g, 0.624 mmol) and the resulting reaction mixture was stirred at ambient temperature for 0.5 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). The reaction workup and purification process are similar to that described for compounds 2 and 3. Evaporation of the appropriate fractions gave white compound 4 (1.55 g, 69.53 %) and 5 (0.109g, 4.82 %).

Compound 4 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxy phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxy-methyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo-[2,1-c:2,1-*l*][1,4,7,10,13,16]hexaazacyclo- henicosin -9-yl]-12-methyltetradecan-amide.

Partial ^{1}H NMR : 7.19 (d, 2H, 8.55 hz), 6.89 (d, 2H, 8.55 hz), 5.12 (d, 1H, 1.65 hz), 3.38 (s, 3H, OCH_3).

IR(KBr):-3300-3400 br, 2920, 1660 br, 1625, 1515, 1440, 1385, 1230, 1070 cm^{-1}

ESI MS(ES+): for $C_{49}H_{79}N_7O_{16}$

Calculated : 1022.194

Found : $(M+Na)^+$ = 1044.5 (base peak)

1030.4, 1013.4, 1000.5, 892.5, 567.3

UV(MeOH): λ_{max} : 206, 223, 277 nm (ε = 12258, 8085, 557)

Compound 5 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S)-1-hydroxy-2-(4-hydroxyphenyl)-2-methoxyethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo-[2,1-c:2,1-*l*][1,4,7,10,13,16]hexaazacyclohe-nicosin-9-yl]-12-methyltetradecan-amide.

Partial ^{1}H NMR : 7.25, 7.15 (2 x d, 2H, 8.37 hz), 6.82 (2 x d(merged), 2H, 8.37 hz), 5.12 (br, 1H), 3.42 (2 x s, 6H, 2 x OCH_3) .

IR(KBr): 3300-3400 br, 2915, 1650 br, 1630, 1520, 1445, 1390(sharp),1240, 1080 cm^{-1}

ESI MS(ES+): for $C_{50}H_{81}N_7O_{16}$

Calculated :1036.221

Found : $(M+Na)^+$ = 1058.6 (base peak)

1014.5, 840.5, 567.2.

UV(MeOH): λ_{max}: 205, 223, 275 nm (ε = 11514, 5526, 506)

Compound 6 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3-(1-azinanyl-methyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxy- ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

In a 25 ml oven dried round-bottom flask were placed ornithine-5-benzylmulundocandin 2 (0.1 g, 0.091 mmol), piperidine (0.077 g, 0.91 mmol), paraformaldehyde (0.0546 g, 1.82 mmol), and anhydrous 1,4-dioxane (10 ml) and the ingredients were heated under reflux for 2 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). TLC analysis after 2 hr. showed no starting compound. Reaction mixture was cooled to ambient temperature, the solvent was evaporated under vacuum to leave a crude residue, which was then diluted with water (100 ml) and extracted with n-butanol (3 x 50 ml). The n-butanol extract was washed with water (100 ml) followed by brine (100 ml). Combined organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give impure product, which was then dissolved in minimum amount of methanol (5 ml), adsorbed on silica gel (1:1 w/w), and was subjected to silica gel flash column chromatography. 0-25 % MeOH/$CHCl_3$ was used as 5 % step gradient elution. Evaporation of the appropriate fractions gave white compound 6 (0.03 g, 27.57 %).

Partial ^1H NMR : 7.28-7.41 (m, 5H,-OCH_2Ph), 7.17 (dd, 1H, 8.32 hz & 1.8 hz), 7.0 (d, 1H, 1.8 hz), 6.78 (d, 1H, 8.37 hz), 5.31 (d, 1H, 1.65 hz), 4.68 (s, 2H,-OCH_2Ph), 4.05 (s, 2H; d), 2.7 (m, 4H), 1.45-1.7 (m, 6H).

IR(KBr): 3300-3400 br, 2920, 1660 br, 1630, 1540, 1460, 1260, 1075 cm^{-1}

ESI MS(ES+): for $C_{61}H_{94}N_8O_{16}$

Calculated : 1195.451

Found :$(M+Na)^+$ = 1217.5

1132.5 (base peak), 1088.4, 808.3, 567.2.

UV(MeOH): λ_{max}: 210, 232, 276 nm (ε = 60230, 33362, 4381)

General procedure for the preparation of compounds 7-46:-

To a stirred solution of compound 2, 3 or 4 (1 eq.) in anhydrous 1,4-dioxane (10-40 ml) was slowly added secondary amine (10 eq.) and paraformaldehyde (20 eq.) and the ingredients were heated under reflux(100-120°C) for 2-31 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). The reaction workup and purification process are similar to the described for compound 6. Stoichiometric ratios of starting compound, secondary amine, paraformaldehyde and anhydrous 1,4-dioxane are given in Table-III. Yield, m.p., reaction time, molecular formula and molecular weight of the compounds (7-46) are given in Table-III.

Compound 7 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3-(1-azolanylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxy- ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*f*] [1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^1H NMR : 7.3-7.4 (m, 5H, OCH_2Ph), 7.25 (dd, 1H, 8.55 hz & 1.9 hz), 7.15 (d, 1H, 1.9 hz), 6.85 (d, 1H, 8.55 hz), 5.33 (d, 1H, 1.65 hz), 4.65 (s, 2H,-OCH_2Ph), 4.12 (s, 2H), 3.3 (m, 4H), 2.05 (m, 4H).

IR(KBr): 3300-3400 br, 2930, 1650, 1625, 1530, 1450, 1260, 1080 cm^{-1}

ESI MS(ES+): for $C_{60}H_{92}N_8O_{16}$

Calculated : 1181.424

Found : $(M+Na)^+$ = 1204.7

1132.5 (base peak),1056.5,567.2.

UV(MeOH): λ_{max}: 207, 231, 280 nm (ε = 49807, 15214, 3515)

Compound 8 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3,5-di(1-azo- lanylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1-R)-1-hydroxy-ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*f*] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.41 (m, 5H, OCH_2Ph), 7.09 (s, 2H), 5.33 (br, 1H), 4.68 (s, 2H, OCH_2Ph), 4.13 (s, 4H), 3.1 (m, 8H), 1.95 (m, 8H).

IR(KBr): 3300-3400 br, 2930, 1650, 1625, 1530, 1450, 1260, 1080 cm^{-1}

ESI MS(ES+): for $C_{65}H_{101}N_9O_{16}$

Calculated : 1264.557

Found : $(M+Na)^+$ = 1287.6

1215.5, 1144.5 (base peak),567.1.

Compound 9 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3-(4-(2-flurophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-tri- hydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxo- perhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetra- decanamide.

Partial ^{1}H NMR : 7.28-7.41 (m, 5H, OCH_2Ph), 7.17 (dd, 1H, 8.11 hz & 1.86 hz), 7.0-7.15 (m, 5H), 6.8 (d, 1H, 8.11 hz), 5.32 (d, 1H, 1.8 hz), 4.67 (s, 2H, OCH_2Ph), 3.85 (s, 2H), 3.18 (m, 4H), 2.82 (m, 4H) .

IR(KBr): 3300-3400 br, 2910, 1640 br, 1615, 1515, 1490(sharp), 1440, 1225, 1060 cm^{-1}

ESI MS(ES+): for $C_{66}H_{96}FN_9O_{16}$

Calculated : 1290.527

Found : $(M+Na)^+$ = 1312.6

1290.7, 1132.6 (base peak),1088.4, 567.0.

UV(MeOH): λ_{max}: 207, 231, 276 nm (ε = 41469, 14667, 4107)

Compound 10 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3,5-di(4-(2-flurophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-trihy- droxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhy- drodiazolo[2,1-c:2,1-/][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.41 (m, 5H, OCH_2Ph), 7.16 (s, 2H), 7.0-7.15 (m, 8H), 5.32 (d, 1H, 1.8 hz), 4.67 (s, 2H, OCH_2Ph), 3.9 (s, 4H), 3.2 (br, 8H), 2.9 (br, 8H).

IR(KBr): 3300-3400 br, 2910, 1660 br, 1620, 1520, 1490, 1440, 1235, 1060 cm^{-1}

ESI MS(ES+): for $C_{77}H_{109}F_2N_{11}O_{16}$

Calculated : 1482.763

Found : $(M+Na)^+$ = 1504.9

1483.0, 1324.7, 1194.7, 1146.6, 567.3.

UV(MeOH): λ_{max} : 207, 235, 278 nm (ε = 40426, 11675, 2626)

Compound 11 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3-(4-(2-chlorophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-tri- hydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoper- hydrodiazolo[2,1-c:2,1-*f*][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecana- mide.

Partial ^{1}H NMR : 7.28-7.40, 7.15-7.21, 7.05-7.12 (3 x m, 11H, Ar-H), 6.81 (d, 1H, 8.01 hz, Ar-H), 5.31 (d, 1H, 1.86 hz), 4.67 (s, 2H, OCH_2Ph), 3.88 (s, 2H), 3.18 (br, 4H), 2.9 (br, 4H).

IR(KBr): 3350-3450 br, 2935, 1650 br, 1630, 1530, 1450, 1260, 1130, 1080 cm^{-1}

ESI MS(ES+): for $C_{66}H_{96}ClN_9O_{16}$

Calculated : 1306.982

Found : $(M+Na)^+$ = 1329.6

1308.5, 1198.8, 132.7 (base peak).

UV(MeOH): λ_{max} : 209, 249, 276 nm (ε = 44379, 8061, 3572)

Compound 12 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3,5-di(4-(2-chlorophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxy-ethyl)-2,11,15-trihy-droxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhy- drodiazolo[2,1-c:2,1-*f*][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.40, 7.15-7.12, 7.06-7.13 (3 x m, 15H, Ar-H), 5.33 (br, 1H), 4.67 (s, 2H, OCH_2Ph), 3.87 (s, 4H), 3.18 (br, 8H), 2.95 (br, 8H) .

IR(KBr): 3350-3450 br, 2930, 1645 br, 1630, 1530, 1450, 1260, 1130, 1075 cm^{-1}

ESI MS(ES+): for $C_{77}H_{109}Cl_2N_{11}O_{16}$

Calculated : 1515.672

Found : $(M+Na)^+$ = 1538.7

1144.3 (base peak),567.4.

Compound 13 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxy-3-(4-(3-trifluromethylphenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihy- droxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhy- drodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR :7.28-7.45 (m, 5H, OCH_2Ph), 7.18-7.26(m, 4H), 7.15 (dd, 1H, 8.13 hz & 1.86 hz),7.1 (d, 1H, 1.86 hz), 6.8 (d, 1H, 8.13 hz), 5.32 (d, 1H, 1.86 hz),4.68(s, 2H, OCH_2Ph), 3.8 (s, 2H), 2.85 (br, 8H).

^{13}C NMR Spectrum :

176.82, 174.90, 174.23, 174.09, 173.56, 172.72, 170.74, 159.17, 153.73, 153.65, 140.71, 133.76, 133.35, 133.12, 132.93, 131.67, 130.70, 130.08, 129.66, 129.39, 128.44, 124.11, 123.53, 121.13, 117.53, 113.82, 81.45, 77.57, 76.85, 76.57, 72.22, 71.04, 70.68, 69.04, 64.18, 63.26, 62.07, 60.36, 59.16, 57.88, 56.43, 54.67, 54.28, 53.64, 51.89, 39.84, 39.45, 38.56, 37.64, 36.46, 35.96, 31.89, 31.58, 31.47, 31.36, 31.11, 28.99, 27.85, 20.57, 20.46, 12.56, 12.01.

IR(KBr): 3350-3450 br, 2930, 1660 br, 1635, 1540, 1455, 1330, 1260, 1180, 1130, 1075 cm^{-1}

ESI MS(ES+): for $C_{67}H_{96}F_3N_9O_{16}$

Calculated : 1340.535

Found :$(M+Na)^+$=1362.6

1266.6, 1132.6 (base peak), 1024.6, 808.3, 567.0.

UV(MeOH): λ_{max} : 208, 240, 255 nm (ε = 4902, 904, 1609)

Compound 14 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3-(4-(1,3-diazin-2-yl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl-1,2-dihydroxyethyl)-2,11,15-trihy- droxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoper- hydrodiazolo[2,1-c:2,1-*f*][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradeca-namide.

Partial ^{1}H NMR : 8.36 (d, 2H, 7.8 hz), 7.29-7.41 (m, 5H, OCH_2Ph), 7.19 (dd, 1H, 8.01 hz & 1.86 hz, Ar-H), 7.08 (d, 1H, 1.86 hz, Ar-H), 6.81 (d, 1H, 8.01 hz, Ar-H), 6.65 (t, 1H, 9.3 hz & 4.5 hz, Ar-H), 5.31 (d, 1H, 1.53 hz), 4.68 (s, 2H, OCH_2Ph), 3.85 (s, 2H), 3.95 (br. 4H), 2.75 (br, 4H).

IR(KBr): 3350-3450 br, 2940, 1660 br, 1630, 1590(s), 1550, 1450, 1390, 1365, 1270, 1075 cm^{-1}

ESI MS(ES+): for $C_{64}H_{95}N_{11}O_{16}$

Calculated : 1274.512

Found :$(M+Na)^+$ = 1296.5

1274.8, 1167.7, 1132.7 (base peak), 1088.6, 567.3.

Compound 15 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3,5-di(4-(1,3-diazin-2-yl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl-1,2-dihydroxyeth-yl)-2,11,15-trihydro- xy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodi- azolo [2,1-c:2,1-*f*] [1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 8.35 (d, 4H, 7.8 hz, Ar-H), 7.26-7.41 (m, 5H, OCH_2Ph), 7.13 (s, 2H), 6.63 (t, 2H, 9.6 hz, 4.8 hz, Ar-H), 5.31 (br.s, 1H), 4.68 (s, 2H, OCH_2Ph), 3.9 (s, 4H), 3.95 (br. 8H), 2.75 (br., 8H).

IR(KBr): 3350-3450 br, 2925, 1660 br, 1630, 1590(s), 1550, 1450, 1390, 1360, 1265, 1080 cm^{-1}

ESI MS(ES+): for $C_{73}H_{107}N_{15}O_{16}$

Calculated : 1450.773

Found :$(M+Na)^+$ = 1472.7

1451.7,1308.4, 1144.6(base peak), 567.2.

Compound 16 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(3-(4-(4-flurophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo [2,1-c:2,1-/] [1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.41 (m, 5H, OCH_2Ph), 7.18 (dd, 1H, 8.40 hz & 1.53 hz, Ar-H), 7.08 (d, 1H, 1.53 hz, Ar-H), 7.0 (d, 4H, 8.16 hz, Ar-H), 6.8 (d, 1H, 8.40 hz, Ar-H), 5.33 (d, 1H, 1.5 hz), 4.68 (s, 2H, OCH_2Ph), 3.85 (s, 2H), 3.20 (br., 4H), 2.80 (br., 4H).

IR(KBr): 3350-3450 br, 2920, 1645 br, 1615, 1509, 1430, 1225, 1065 cm^{-1}

ESI MS(ES+): for $C_{66}H_{96}FN_9O_{16}$

Calculated : 1290.527

Found :$(M+Na)^+$ = 1312.4

1291.7, 1182.6, 1164.7, 1132.5 (base peak), 1088, 567.1.

Compound 17 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3,5-di(4-(4-flurophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15–trihydro- xy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodi-azolo [2,1-c:2,1-/] [1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.41 (m, 5H, OCH_2Ph), 7.14 (s, 2H, Ar-H),7.0 (d, 8H, 7.41 hz, Ar-H), 5.33 (d, 1H, 1.8 hz), 4.68 (s, 2H, OCH_2Ph), 3.85 (s, 4H), 3.22 (br, 8H), 2.83 (br, 8H).

IR(KBr): 3350-3450 br, 2920, 1645 br, 1615, 1509, 1430, 1225, 1065 cm^{-1}

ESI MS(ES+): for $C_{77}H_{109}F_2N_{11}O_{16}$

Calculated : 1482.763

Found :$(M+Na)^+$ = 1504.8

1482.9, 1225.7, 1268.6, 1195.8, 1144.7, 1088.6, 567.3.

UV(MeOH): λ_{max} : 210, 233, 285 nm (ε = 75574, 36321, 8063)

Compound 18 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxy-3-(4-phenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c: 2,1-/] [1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.41(m,5H, OCH_2Ph), 7.21-7.27 (m, 2H, Ar-H), 7.19 (dd, 1H, 8.40 hz & 2.16 hz, Ar-H), 7.08 (d,1H, 2.16 hz), 7.02 (d, 2H, 8.40 hz), 6.90 (t, 1H, 7.20 hz), 6.80 (d, 1H, 8.40 hz), 5.31 (d, 1H, 2.25 hz), 4.68 (s, 2H, OCH_2Ph), 3.85 (s, 2H), 3.27 (br, 4H), 2.80 (br, 4H,).

IR(KBr): 3300-3400 br, 2910, 1645 br, 1610, 1515, 1430, 1215, 1060 cm^{-1}

ESI MS(ES+): for $C_{66}H_{97}N_9O_{16}$

Calculated : 1272.537

Found :$(M+Na)^+$= 1294.7

1272.4, 1132.5 (base peak), 1089.9, 808.5, 567.2.

UV(MeOH): λ_{max} : 207, 230, 246, 279 nm (ε = 47454, 14338, 12697, 3314)

Compound 19 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy- 2-(4-hydroxy-3,5-di(4-phenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo- [2,1-c:2,1-/][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.25-7.41 (m, 9H, OCH_2Ph), 7.14 (s, 2H, Ar-H), 7.03 (d, 4H, 8.70 hz, Ar-H), 6.88 (tt, 2H, 7.5 hz & 1.2 hz, Ar-H), 5.31 (d, 1H, 1.53 hz), 4.68 (s, 2H, OCH_2Ph), 3.85 (s, 4H), 3.87 (br, 8H,), 2.80 (br, 8H).

IR(KBr): 3300-3400 br, 2910, 1650 br, 1625, 1525, 1440, 1220, 1060 cm^{-1}

ESI MS(ES+): for $C_{77}H_{111}N_{11}O_{16}$

Calculated : 1446.782

Found :$(M+Na)^+$= 1468.8

1446.8, 1306.8, 1176.8, 1144.6 (base peak), 1036.7, 567.2.

UV(MeOH): λ_{max} : 208, 248, 282 nm (ε = 65504, 32883, 4472)

Compound 20 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3-dibenzyl aminomethyl-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxy- ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*f*] [1,4,7,10, 13, 16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.42 (m, 15H, OCH_2Ph, 2 x NCH_2Ph), 7.17 (dd, 1H, 8.64 hz & 2.16 hz, Ar-H), 7.09 (d, 1H, 2.16 hz, Ar-H), 6.79 (d, 1H, 8.64 hz, Ar-H), 5.31 (d, 1H, 1.53 hz), 4.68 (s, 2H, OCH_2Ph), 3.63-3.7 (2 x s, 6H).

^{13}C NMR Spectrum :

176.83, 174.96, 174.15, 174.08, 173.5, 172.66, 170.62, 158.97, 140.66, 139.11, 134.0, 131.51, 130.44, 130.02, 129.76, 129.67, 129.57, 129.34, 128.86, 124.07, 117.41, 81.46, 77.39, 76.77, 76.48, 72.21, 72.12, 71.05, 70.63, 69.01, 64.09, 63.15, 59.53, 59.24, 57.88, 56.74, 56.36, 53.55, 51.99, 39.80, 39.38, 38.54, 37.60, 36.43, 35.95, 31.87, 31.55, 31.42, 31.36, 31.06, 28.96, 27.83, 20.42, 12.53, 11.98.

IR(KBr): 3300-3400 br, 2910, 1640 br, 1615, 1515, 1430, 1240, 1060 cm^{-1}

ESI MS(ES+): for $C_{70}H_{98}N_8O_{16}$

Calculated : 1307.582

Found :$(M+Na)^+$ = 1330.7

1132.6 (base peak),1024.4, 567.2.

UV(MeOH): λ_{max} : 206, 225, 279 nm (ε = 37234, 8761, 15135)

Compound 21 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3-(4-benzyl-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c: 2,1-*f*][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.43 (m, 10H, OCH_2Ph, -NCH_2Ph),7.18 (dd, 1H, 8.64 hz & 1.86 hz, Ar-H), 7.03 (d, 1H, 1.86 hz, Ar-H), 6.78 (d,1H, 8.64 hz, Ar-H), 5.31 (d, 1H, 2.04 hz), 4.68 (s, 2H, -OCH_2Ph), 3.58-3.62 (2 x s, 4H), 3.18, 2.68 (2 x t, 8H).

IR(KBr): 3300-3400 br, 2930, 1650 br, 1625, 1520, 1450, 1390, 1260, 1070 cm^{-1}

ESI MS(ES+): for $C_{67}H_{99}N_9O_{16}$

Calculated : 1286.563

Found :$(M+Na)^+$= 1309.6

1132.5 (base peak), 1088.3, 567.2.

UV(MeOH): λ_{max} : 208, 229, 280 nm (ε = 42242, 12359, 2648)

Compound 22 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3-(4-(2-azinyl)-1,4-diaz- inan-1-ylmethyl)-4-hydroxyphenyl-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodi- azolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 8.1-8.16 (m, 1H, Ar-H), 7.6 (m, 1H, Ar-H), 7.3-7.45 (m, 5H, -OCH_2Ph), 7.18 (dd, 1H, 8.37 hz & 1.41 hz, Ar-H), 7.08 (d, 1H, 1.41 hz, Ar-H), 6.89 (m, 1H, Ar-H), 6.8 (d, 1H, 8.37 hz, Ar-H), 6.75 (m, 1H, Ar-H), 5.31 (d, 1H, 1.53 hz), 4.68 (s, 2H, -OCH_2Ph), 3.8 (s, 2H), 3.6 (m, 4H), 2.72 (m, 4H).

IR(KBr): 3300-3400 br, 2930, 1640 br, 1620, 1520, 1430, 1375, 1235, 1060 cm^{-1}

ESI MS(ES+): for $C_{65}H_{96}N_{10}O_{16}$

Calculated : 1273.524

Found :$(M+Na)^+$ = 1295.7

1273.7, 1132.5, 808.4, 567.2.

UV(MeOH): λ_{max} : 208, 248, 299 nm (ε = 43844, 27725, 5899)

Compound 23 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxy-3-(4-(4-methylphenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo- [2,1-c:2,1-/] [1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.29-7.43 (m, 5H, -OCH_2Ph), 7.18 (dd, 1H, 8.64 hz & 1.53 hz), 7.06-7.12 (m, 3H, Ar-H), 6.93 (d, 2H, 8.64 hz, Ar-H), 6.79 (d, 1H, 8.64 hz, Ar-H),

5.31 (d, 1H, 1.53 hz), 4.68 (s, 2H, -OCH_2Ph), 3.81 (s, 2H), 3.2 (br, 4H), 2.78 (br, 4H), 2.38 (s, 3H, Ar-CH_3).

IR(KBr): 3300-3400 br, 2930, 1640 br, 1620, 1520, 1430, 1375, 1235, 1060 cm^{-1}

ESI MS(ES+): for $C_{67}H_{99}N_9O_{16}$

Calculated : 1286.583

Found :$(M+Na)^+$ = 1309.6

1273.7, 1132.5, 808.4, 567.2.

UV(MeOH): λ_{max} : 209, 230, 247, 279 nm (ε = 71176, 61764, 20808, 5147)

Compound 24 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxy-3,5-di(4-(4-methylphenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydro- xy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodi- azolo [2,1-c:2,1-/] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^1H NMR : 7.29-7.43 (m, 5H, -OCH_2Ph), 7.14 (s, 2H), 7.1 (d, 4H, 8.64 hz), 6.92 (d, 4H, 8.64 hz), 5.33 (d, 1H, 1.86 hz), 4.68 (s, 2H, -OCH_2Ph), 3.82 (s, 4H), 3.21 (br, 8H), 2.73 (br, 8H), 2.29 (s, 6H, 2 x Ar-CH_3).

IR(KBr): 3350-3450 br, 2940, 1655 br, 1630, 1519(sharp), 1450, 1385(sharp), 1060 cm^{-1}

ESI MS(ES+): for $C_{79}H_{115}N_{11}O_{16}$

Calculated : 1474.835

Found :$(M+Na)^+$ = 1496.8

1474.6, 1389.1, 1320.5, 1144.4 (base peak), 1036.4, 567.4.

UV(MeOH): λ_{max} : 210, 242, 284 nm (ε = 62037, 26909, 5900)

Compound 25 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3,5-di(4-(4-azinyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-

5,8,14,19,22,25-hexaoxoperhydrodiazolo- [2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 8.15-8.22 (m, 4H, Ar-H), 7.25-7.43 (m, 5H, -OCH_2Ph), 7.14 (s, 2H, Ar-H), 7.0 (m, 4H, Ar-H), 5.31 (br, 1H), 4.68 (s, 2H, -OCH_2Ph), 3.81 (s, 4H), 3.65 (br, 8H) , 2.73 (br, 8H) .

IR(KBr): 3350-3450 br, 2920, 1650 br, 1610, 1540, 1510, 1440, 1385(sharp), 1230, 1070 cm^{-1}

ESI MS(ES+): for $C_{75}H_{109}N_{13}O_{16}$

Calculated : 1448.457

Found :$(M+Na)^+$ = 1470.6

1449.6, 1307.5, 1199.4, 1177.8, 1036.3.

UV(MeOH): λ_{max} : 208, 237, 262 nm (ε = 75379, 10463, 41034)

Compound 26:

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3-(4-(1-azinanyl)-1-azina- nylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c: 2,1-/] [1,4,7,10,13,16]-hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.45 (m, 5H, -OCH_2Ph), 7.18 (dd, 1H, 8.64 hz & 1.86 hz, Ar-H), 7.06 (d, 1H, 1.86 hz, Ar-H), 6.8 (d, 1H, 8.64 hz, Ar-H), 5.02 (d, 1H, 1.86 hz), 4.68 (s, 2H, -OCH_2Ph), 3.78 (s, 2H), 2.89-3.28 (m, 9H), 1.7-1.9 (m, 10H).

IR(KBr): 3300-3400 br, 2940, 1660 br, 1635, 1518, 1460, 1370 br, 1075 cm^{-1}

ESI MS(ES+): for $C_{66}H_{103}N_9O_{16}$

Calculated : 1278.584

Found :$(M+Na)^+$ = 1300.5

1132.4 (base peak), 1102.7, 1024, 567.2.

UV(MeOH): λ_{max} : 208, 225, 279 nm (ε = 46029, 13780, 1619)

Compound 27 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(3-(4-(2,6-dimethylphenyl)-1,4-diazinan-1-ylmethyl)-4-

hydroxyphenyl)ethyl)-2,11,15-trihydro- xy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodi- azolo [2,1-c:2,1-*l*] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.29-7.42 (m, 5H, -OCH_2Ph), 7.18 (dd, 1H, 8.55 hz & 1.32 hz, Ar-H), 7.09 (d, 1H, 1.32 hz, Ar-H), 6.9-7.03 (m, 3H, Ar-H), 6.81 (d, 1H, 8.55 hz, Ar-H), 5.31 (br, 1H), 4.68 (s, 2H, -OCH_2Ph), 3.91 (s, 2H), 3.2 (br, 4H), 2.82 (br, 4H), 2.38 (s, 6H, 2 x Ar-CH_3).

^{13}C NMR Spectrum :

176.82, 174.95, 174.20, 174.03, 173.53, 172.67, 170.63, 159.28, 149.74, 140.71, 138.70, 133.76, 130.98, 130.84, 130.06, 129.64, 129.36, 127.85, 127.35, 122.66, 117.51, 81.42, 77.57, 76.79, 76.54, 72.22, 71.04, 70.74, 69.04, 64.16, 63.24, 62.09, 59.25, 57.91, 56.32, 55.62, 54.98, 54.73, 53.59, 51.94, 51.11, 39.81, 39.45, 38.56, 37.61, 36.46, 35.93, 31.89, 31.58, 31.47, 31.36, 31.11, 28.99, 27.85, 20.65, 20.51, 20.46, 12.56, 11.98.

IR(KBr): 3300-3400 br, 2935, 1660 br, 1625, 1530, 1450, 1385, 1260, 1070 cm^{-1}

ESI MS(ES+): for $C_{68}H_{101}N_9O_{16}$

Calculated : 1300.590

Found :$(M+Na)^+$ = 1322.5

1132.5 (base peak), 567.2.

UV(MeOH): λ_{max} : 208, 226, 267 nm (ε = 37979, 14394, 2709)

Compound 28 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(3,5-di(4-(2,6-dimethylphenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)ethyl)-2,11,15-trihy- droxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhy- drodiazolo[2,1-c:2,1-*l*] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.42 (m, 5H, -OCH_2Ph), 7.21 (s, 2H, Ar-H), 6.98-7.2 (m, 6H, Ar-H), 5.33 (br, 1H), 4.68 (s, 2H, -OCH_2Ph), 4.11 (s, 4H), 3.29 (br, 8H), 3.05 (br, 8H), 2.40 (s, 12H, 4 x Ar-CH_3).

IR(KBr): 3350-3450 br, 2920, 1670 br, 1630, 1535, 1460, 1390(sharp), 1220, 1070 cm^{-1}

ESI MS(ES+): for $C_{81}H_{119}N_{11}O_{16}$

Calculated : 1502.889

Found :$(M+Na)^+$ = 1525.6

1503.7, 1334.6, 1204.6, 1144.6 (base peak), 668.4.

UV(MeOH): λ_{max} : 211, 226, 257, 282 nm (ε = 58787, 26424, 8513, 5187)

Compound 29 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxy-3-(4-(1-phenylethyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo- [2,1-c:2,1-*l*] [1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.45 (m,10H, -OCH_2Ph & -$CH(CH_3)$Ph), 7.17 (dd, 1H, 8.55 hz & 1.32 hz, Ar-H), 7.03 (d, 1H, 1.32 hz, Ar-H), 6.77 (d, 1H, 8.55 hz, Ar-H), 5.31 (d, 1H, 1.98 hz), 4.68 (s, 2H, -OCH_2Ph), 3.75 (s, 2H), 3.8 (q, 1H, 7.89 hz), 2.6-2.79 (m, 8H), 1.45 (d, 3H, 7.89 hz).

^{13}C NMR Spectrum :

176.80, 174.92, 174.08, 173.50, 172.66, 170.65, 159.20, 144.93, 144.51, 140.70, 133.68, 130.41, 130.18, 130.05, 129.63, 129.34, 129.15, 129.08, 123.63, 117.41, 81.43, 77.49, 76.81, 76.55, 72.18, 72.12, 71.02, 70.66, 69.01, 67.13, 64.13, 63.19, 62.09, 59.21, 57.85, 56.43, 54.68, 54.29, 53.58, 52.38, 51.93, 51.41, 50.99, 46.62, 39.80, 39.41, 38.54, 37.60, 36.43, 35.95, 31.87, 31.55, 31.45, 31.36, 31.10, 28.96, 27.83, 20.94, 20.45, 12.56, 11.98.

IR(KBr): 3300-3400 br, 2920, 1660 br, 1625, 1530, 1455, 1390(sharp), 1260, 1070 cm^{-1}

ESI MS(ES+): for $C_{68}H_{101}N_9O_{16}$

Calculated : 1300.590

Found :$(M+Na)^+$ = 1323.6

1300.6, 1132.5, 808.5, 567.3.

UV(MeOH): λ_{max} : 206, 223, 279 nm (ε = 47065, 14834, 1881)

Compound 30 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(3,5-di(4-(1-phenylethyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl) ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodi- azolo [2,1-c:2,1-*f*] [1,4,7,10,13,16]-hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.22-7.40 (m, 15H, -OCH_2Ph & 2 x -$CH(CH_3)$Ph), 6.84 (s, 2H, Ar-H), 5.02 (br, 1H), 4.45 (s, 2H, -OCH_2Ph), 3.52 (s, 4H), 3.42 (q, 2H, 7.8 hz), 2.3-2.55 (m, 16H), 1.28 (d, 6H, 7.8 hz).

IR(KBr): 3300-3450 br, 2920,1655,1625,1525,1450, 1385(sharp), 1255, 1070 cm^{-1}

ESI MS(ES+): for $C_{81}H_{119}N_{11}O_{16}$

Calculated : 1502.889

Found :$(M+ Na)^+$ = 1525.7

1502.8, 1334.6, 1204.6, 1144.4, 763.5, 668.0, 567.0.

UV(MeOH): λ_{max} : 205, 219, 284 nm (ε = 50300, 7314, 1833)

Compound 31 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3-benzyl(tert.butyl)amino- methyl-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhyd-rodiazolo[2,1-c:2,1-*f*] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.15-7.45 (m, 10H, -OCH_2Ph & -NCH_2Ph), 7.05 (dd, 1H, 8.37 hz & 1.41 hz, Ar-H), 6.95 (d, 1H, 1.41 hz, Ar-H), 6.55 (d, 1H, 8.37 hz, Ar-H), 5.32 (d, 1H, 2.1 hz), 4.68 (s, 2H,-OCH_2Ph), 4.09 (s, 2H), 3.89 (s, 2H), 1.42 (s, 9H, 3 x e or -$C(CH_3)_3$).

IR(KBr): 3300-3400 br, 2920, 1660 br, 1625, 1525, 1440, 1375(sharp), 1250, 1070 cm^{-1}

ESI MS(ES+): for $C_{67}H_{100}N_8O_{16}$

Calculated : 1273.565

Found :$(M+Na)^+$ = 1296.6

1132.5 (base peak), 567.3.

UV(MeOH): λ_{max} : 210, 226, 280 nm (ε = 76304, 28418, 4257)

Compound 32 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3-benzyl(isopropyl)amino- methyl-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hy- droxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhyd-rodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.45 (m, 10H, -OCH_2Ph & -NCH_2Ph), 7.16 (dd, 1H, 8.55 hz & 1.98 hz, Ar-H), 7.05 (d, 1H, 1.98 hz, Ar-H), 6.74 (d, 1H, 8.55 hz, Ar-H), 5.32 (br, 1H), 4.68 (s, 2H, OCH_2Ph), 3.9, 3.65 (2 x s, 4H), 3.1 (m, 1H), 1.22 (m, 6H).

IR(KBr): 3300-3400 br, 2935, 1680-1625 br, 1540, 1450, 1385(sharp), 1260, 1075 cm^{-1}

ESI MS(ES+): for $C_{66}H_{98}N_8O_{16}$

Calculated : 1259.538

Found :$(M+Na)^+$ = 12.81.8

1132.4 (base peak), 567.1.

UV(MeOH): λ_{max} : 207, 231, 280 nm (ε = 58232, 10790, 2997)

Compound 33 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3,5-di(benzyl(iso-propyl)aminomethyl-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.43 (m, 15H, -OCH_2Ph & 2 x -NCH_2Ph), 7.03 (s, 2H, Ar-H), 5.33 (br, 1H), 4.68 (s, 2H, -OCH_2Ph), 3.87, 3.63 (2 x s, 8H), 3.0 (m, 2H), 1.2-1.3 (m, 12H).

IR(KBr): 3400-3500 br, 2945, 1680- 1630 br, 1540, 1460, 1385(sharp), 1260, 1080 cm^{-1}

ESI MS(ES+): for $C_{77}H_{113}N_9O_{16}$

Calculated : 1420.784

Found :$(M)^+$ = 1420.9

1293.4, 1144.9(base peak), 1024.4, 996.2, 648.1.

UV(MeOH): λ_{max} pH: 207, 227, 282 nm (ε = 67687, 10661, 1465)

Compound 34 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S)-2-(3-(1-azinanylmethyl)-4-hydro- xyphenyl)-2-benzyloxy-1-hydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxy- thyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*f*][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.25-7.41 (m, 10H, 2 x OCH_2Ph), 7.2 (dd, 1H, 8.5 hz & 1.85 hz, Ar-H), 7.14 (d, 1H, 1.85 hz, Ar-H), 6.87 (d, 1H, 8.5 hz), 5.35 (br, 1H), 4.6 (s, 4H, 2 x -OCH_2Ph), 4.14 (s, 2H), 3.12 (m, 4H), 2.04 (m, 6H).

IR(KBr): 3300-3400 br, 2915, 1650, 1620, 1530, 1440, 1250, 1070 cm^{-1}

ESI MS(ES) : for $C_{68}H_{100}N_8O_{16}$

Calculated : 1285.576

Found : $(M+Na)^+$ = 1308.6(base peak), 567.3

UV(MeOH):- λ_{max} : 211, 255, 288 nm (ε = 73984, 20087, 5142)

Compound 35 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-2-(3,5-di(1-azinanylmethyl)-4-hydroxyphenyl)-1-hydroxyethyl)-2,11,15-trihydroxy-6-(1R)-1-hydroxy- ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*f*] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.45 (m, 10H, 2 x -OCH_2Ph), 7.21 (2 x s, 2H, Ar-H), 5.32 (br, 1H), 4.65 (s, 4H, 2 x -OCH_2Ph), 4.11 (m, 4H), 2.98 (m, 8H), 1.98 (m, 12H).

IR(KBr): 3300-3400 br, 2910, 1650, 1625 br,1530, 1440, 1250, 1070 cm^{-1}

ESI MS(ES+): for $C_{74}H_{111}N_9O_{16}$

Calculated : 1382.735

Found :$(M+Na)^+$ = 1404.8 (base peak)

1382.6, 1320.7, 1189.4, 1081.6, 808.5, 567.3.

UV(MeOH): λ_{max} : 209, 234, 290 nm (ε = 46021, 9127, 3989)

Compound 36:

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S)-2-(3-(1-azolanylmethyl)-4-hydro- xyphenyl)-2-benzyloxy-1-hydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxy- ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.25-7.41 (m, 10H, 2 x -OCH_2Ph), 7.25 (dd, 1H, 8.5 hz & 1.9 hz, Ar-H), 7.14 (d, 1H, 1.9 hz, Ar-H), 6.87 (d, 1H, 8.5 hz, Ar-H),5.31 (br, 1H),4.67(s, 4H, 2 x-OCH_2Ph), 4.13 (s, 2H), 3.35 (m, 4H), 2.1 (m, 4H).

IR(KBr): 3300-3400 br, 2925, 1650, 1620, 1535, 1450, 1250, 1075 cm^{-1}

ESI MS(ES+): for $C_{67}H_{98}N_8O_{16}$

Calculated : 1271.549

Found :$(M+Na)^+$ = 1293.6 (base peak)

1159.0, 1114.5, 734.9.

UV(MeOH): λ_{max} : 211, 230, 278 nm (ε = 64015, 27056, 6845)

Compound 37:

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-2-(3,5-di(1-azolanylmethyl)-4-hydroxyphenyl)-1-hydroxyethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxy ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.41 (m, 10H, 2 x -OCH_2Ph), 7.10, 7.14 (2 x s, 2H, Ar-H), 5.33 (br, 1H), 4.68 (s, 4H, 2 x -OCH_2Ph), 4.18 (m, 4H), 3.12 (m, 8H), 2.05 (m, 8H).

IR(KBr): 3320-3420 br, 2920, 1660-1630 br, 1530, 1465, 1080 cm^{-1}

ESI MS(ES+): for $C_{72}H_{107}N_9O_{16}$

Calculated : 1354.682

Found :$(M+Na)^+$ = 1376.6 (base peak)

1354.5, 1305.6, 1175.7, 1067.5, 653.8.

UV(MeOH): λ_{max} : 208, 230, 289 nm (ε = 64738, 12888, 5155)

Compound 38:

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-1-hyd- roxy-2-(4-hydroxy-3-(4-methyl-1-azinanylmethyl) phenyl) ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo-[2,1-:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.2-7.41 (m, 10H, 2 x -OCH_2Ph), 7.17 (dd, 1H, 8.32 hz & 1.8 hz, , Ar-H), 7.0 (d, 1H, 1.8 hz, Ar-H), 6.78 (d, 1H, 8.32 hz, Ar-H), 5.31 (br, 1H), 4.68 (s, 4H, 2 x -OCH_2Ph), 4.1 (s, 2H), 2.65 (m, 4H), 1.85 (m, 4H), 1.28 (m,1H), 1.06 (m, 3H, $CHCH_3$).

IR(KBr)(acetate salt) :-3330-3400 br, 2950, 1717, 1635, 1530, 1450, 1250, 1065, 1065 cm^{-1}

ESI MS(ES+): for $C_{69}H_{102}N_8O_{16}$

Calculated : 1299.602

Found :$(M+Na)^+$ = 1321.7 (base peak), 559.47.

UV(MeOH): λ_{max} : 208, 230, 284 nm (ε = 49233, 17260, 3249)

Compound 39:

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-1-hydroxy-2-(4-hydroxy-3,5-di(4-methyl-1-azinanylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodia-zolo [2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.25-7.41 (m, 10H, 2 x -OCH_2Ph), 7.09, 7.21 (2 x s, 2H, Ar-H), 5.33 (br, 1H), 4.68 (s, 4H, 2 x OCH_2Ph), 4.11 (s, 4H), 2.7 (m, 8H), 1.85 (m, 8H), 1.25 (m, 2H), 1.06 (m, 6H).

IR(KBr)(915/78.D,acetate salt): 3350-3450 br, 2960, 1715(sharp), 1635, 1530, 1455, 1060 cm^{-1}

ESI MS(ES+): for $C_{76}H_{115}N_9O_{16}$

Calculated : 1430.659

Found :$(M+Na)^+$ = 1432.9

1411.6, 1333.6, 1203.7, 1095.7, 808.3, 559.4, 667.6.

UV(MeOH): λ_{max} : 206, 237, 288 nm (ε = 1463, 153, 29)

Compound 40 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-1-hydroxy-2-(4-hydroxy-3-(4-(3-trifluromethylphenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyl-tetradecanamide.

Partial ^{1}H NMR : 7.28-7.5 (m, 10H, 2 x -OCH_2Ph), 7.15-7.27 (m, 4H, Ar-H), 7.12 (dd, 1H, 8.22 hz, & 1.38 hz), 7.05 (d, 1H, 1.38 hz, Ar-H), 6.85 (d, 1H, 8.22 hz , Ar-H), 5.32 (br, 1H), 4.68 (s, 4H, 2 x -OCH_2Ph), 3.85 (s, 2H), 2.81 (m, 8H).

IR(KBr): 3300-3400 br, 2910, 2330(sharp), 1640 br, 1610, 1515, 1430, 1300, 1220, 1065 cm^{-1}

ESI MS(ES+): for $C_{74}H_{102}F_3N_9O_{16}$

Calculated : 1430.659

Found :$(M+Na)^+$ = 1452.7

1222.2 (base peak), 567.3.

Compound 41 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-1-hydroxy-2-(4-hydroxy-3,5-di(4-(3-trifluromethylphenyl)-1,4-diazinan-1-ylmethyl)phenyl)- ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14, 19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.25-7.45 (m, 10H, 2 x -OCH_2Ph), 7.02-7.2 (m,10H, Ar-H), 5.33 (br, 1H), 4.68 (s, 4H, 2 x -OCH_2Ph), 3.8 (s, 4H), 2.75-2.9 (m, 16H).

IR(KBr): 3300-3400 br, 2925, 1660 br, 1610, 1540, 1455, 1330, 1260, 1075 cm^{-1}

ESI MS(ES+): for $C_{86}H_{115}F_6N_{11}O_{16}$

Calculated : 1672.903

Found :$(M+Na)^+$ = 1695.5

1222.6, 567.1.

UV(MeOH): λ_{max} : 212, 255, 282, 305 nm (ε = 41827, 20244, 4567, 2018)

Compound 42 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-2-(3-dibenzylaminomethyl-4-hydroxyphenyl)-1-hydroxyethyl)-2,11,15-trihydroxy-6-((1R)-1-hydro- xyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.22-7.44 (m, 20H, 2 x -OCH_2Ph & -$N(CH_2Ph)_2$), 7.11 (dd, 1H, 8.6 hz & 2.2 hz, Ar-H), 7.08 (d, 1H, 2.2 hz, Ar-H), 6.81 (d, 1H, 8.6 hz, Ar-H), 5.3 (br, 1H), 4.68 (s, 4H, 2 x -OCH_2Ph), 3.6-3.7 (s, 4H), 3.79 (s, 2H).

IR(KBr): 3300-3400 br, 2930, 1650 br, 1615(sharp), 1516, 1435, 1240, 1060 cm^{-1}

ESIMS(ES+): for $C_{77}H_{104}N_8O_{16}$

Calculated : 1397.706

Found : $(M+Na)^+$ = 1421.6

1222.8 (base peak), 1114.1, 768.8, 567.2.

UV(MeOH): λ_{max} : 210, 228, 280 nm (ε = 61484, 15835, 2697)

Compound 43 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(3-(4-(4-fluorophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhydro- diazolo[2,1-c:2,1-/]
[1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.18 (dd, 1H, 8.40 hz & 1.53 hz), 7.08 (d, 1H, 1.53 hz, Ar-H), 7.02 (d, 4H, 8.25 hz, Ar-H), 6.8 (d, 1H, 8.40 hz, Ar-H), 5.12 (d, 1H, 1.5 hz), 3.83 (s, 2H), 3.38 (s , 3H, OCH_3), 3.2 (br, 4H), 2.79 (br, 4H).

IR(KBr): 3300-3400br, 2930, 1645, 1620, 1510, 1440, 1380, 1230, 1070 cm^{-1}

ESI MS(ES+): for $C_{60}H_{92}FN_9O_{16}$

Calculated : 1214.429

Found : $M+Na)^+$ = 1236.7

1124.5, 1056.4 (base peak), 1012.4, 808.4, 567.2.

UV(MeOH): λ_{max} : 205, 230, 282 nm (ε = 35278, 16251, 1477)

Compound 44 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3,5-di(4-(4-fluorophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodia- zolo[2,1-c:2,1-*l*] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide

Partial ^{1}H NMR : 7.13 (s, 2H, Ar-H), 7.0-7.1(m, 8H, Ar-H), 5.12 (br, 1H), 3.82 (s, 4H), 3.38 (s, 3H, OCH_3), 3.21 (br, 8H), 2.78 (br, 8H).

IR(KBr): 3300-3400br, 2930, 1645, 1620, 1510, 1440, 1380, 1230, 1070 cm^{-1}

ESI MS(ES+): for $C_{71}H_{105}F_2N_{11}O_{16}$

Calculated : 1406.665

Found :$(M+Na)^+$ = 1428.9

1249.6, 1068.4 (base peak), 839.8, 567.1.

UV(MeOH): λ_{max} : 207, 215, 234, 284 nm (ε = 46370, 30669, 14068, 2900)

Compound 45 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxy-3-(4-phenyl-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*l*] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.22-7.35 (m, 2H, Ar-H), 7.2 (dd, 1H, 8.22 hz & 1.98 hz, Ar-H), 7.1 (d, 1H, 1.98 hz, Ar-H), 7.02 (m, 2H, Ar-H), 6.9 (m, 1H, Ar-H), 6.81 (d, 1H, 8.22 hz, Ar-H), 5.13 (d, 1H, 1.5 hz), 3.9 (s, 2H), 3.42 (s, 3H, OCH_3), 3.2-3.3 (br, 4H), 2.85-2.95 (br, 4H).

IR(KBr): 3350-3450 br, 2920, 1650 br, 1620, 1530, 1435, 1375, 1220, 1070 cm^{-1}

ESI MS(ES+): for $C_{60}H_{93}N_9O_{16}$

Calculated : 1196.439

Found :$(M+Na)^+$ = 1218.2

1056.4(base peak),1025.1, 893.0, 567.3.

UV(MeOH): λ_{max} : 207, 232, 248, 279 nm (ε = 44536, 15767, 15368, 3562)

Compound 46 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(3,5-di(4-phenyl-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxy ethyl)-20-hydroxymethyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide

Partial ^{1}H NMR : 7.24-7.41 (m, 4H, Ar-H), 7.15 (s, 2H, Ar-H), 7.0 (m, 4H, Ar-H), 6.89 (m, 2H, Ar-H), 5.1 (br, 1H), 3.83 (s, 4H), 3.4 (s, 3H, CH_3), 3.12-3.21 (br, 8H), 2.68-2.95 (br, 8H).

IR(KBr): 3350-3450 br, 2920, 1650 br, 1620, 1530, 1435, 1375, 1220, 1070 cm^{-1}

ESI MS(ES+): for $C_{71}H_{107}N_{11}O_{16}$

Calculated : 1370.684

Found :$(M+Na)^+$ = 1393.0

1232.5, 1054.3 (base peak), 1042.0.

UV(MeOH): λ_{max} : 205, 248, 279 nm (ε = 29408, 8099, 1557)

Compound 47 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-(1H-1,3-diazol-1-yl)-2-(3-(1H-1,3-diazol-1-ylmethyl)-4-hydroxyphenyl)-1-hydroxyethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-ethyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo- [2,1-c:2,1-/][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide

To a stirred solution of ornithine-5-benzylmulundocandin 2 (0.2 g, 0.182 mmol) in anhydrous N,N-dimethylformamide (10 ml) was added imidazole (0.122 g, 1.8 mmol), paraformaldehyde (0.108 g, 3.6 mmol) and heated under reflux for 15 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). The reaction work-up and purification procedure was similar to that of compound 6. Yield of the white solid 47 (0.03 g, 13.42 %).

Partial ^{1}H NMR : 7.8-7.7 (m, 2H, Ar-H), 7.42-7.28 (m, 5H, OCH_2Ph), 6.99-7.1, 7.19 (2 x br, 6Hv), 6.82 (d, 1H, 8.13 hz, Ar-H), 5.32 (s,1H), 4.67 (s , 2H, OCH_2Ph), 3.8 (s, 2H).

ESI MS(ES+): for $C_{62}H_{89}N_{11}O_{16}$

Calculated : 1228.444

Found : $(M+Na)^+$ = 1250.41130.4, 1063.6, 950.8, 805.7, 357.9, 259.1, 229.2(base peak).

UV(MeOH): λ_{max} : 210, 271 nm (ε = 53232, 2538)

TABLE III

Comp. No.	Starting Compound	Secondary Amine	Para-formal-dehyde	Dioxan (ml)/ React. time (hr.)	Comp.No. Yield (g , %)	M.P.(°C)	Mole.Formula/ Mole.Weight.
7&8	Orn-5-benzyl MLD(2) 0.1 g, 0.091 mmol	Pyrrolidin 0.0647 g, 0.91 mmol	0.0546 g, 1.82 mmol	10/4	7 0.025 g, 23.24 8 0.023 g, 19.98	7 145 (dec) 8 NA	7 $C_{60}H_{92}N_8O_{16}$ 1181.424 8 $C_{65}H_{101}N_9O_{16}$ 1264.557
9&10	2 0.2 g, 0.182 mmol	1-(2-Flurophenyl), piperazine 0.328 g, 1.82 mmol	0.109 g, 3.64 mmol	10/6	9 0.083 g, 35.31 10 0.105 g, 38.88	9 169 10 145	9 $C_{66}H_{96}FN_9O_{16}$ 1290.527 10 $C_{77}H_{109}F_2N_{11}O_{16}$ 1482.763
11&12	2 0.3 g, 0.273 mmol	1-(2-Chlorophenyl), piperazine 0.536 g, 2.73 mmol	0.163 g, 5.46 mmol	15/5	11 0.16 g, 44.81 12 0.074 g, 17.87	11 105 12 109-110	11 $C_{66}H_{96}Cl\ N_9O_{16}$ 1306.982 12 $C_{77}H_{109}Cl_2N_{11}O_{16}$ 1515.672

Comp. No.	Starting Compound	Secondary Amine	Para-formal-dehyde	Dioxan (ml)/ React. time (hr.)	Comp.No. Yield (g , %)	M.P.(°C)	Mole.Formula/ Mole.Weight.
13	2 0.2 g, 0.182 mmol	N-(α,α,α-Trifluro -m-tolyl) piperazine 0.419 g, 1.8 mmol	0.109 g, 3.64 mmol	10/5	13 0.165 g, 67.59	13 111	13 $C_{67}H_{96}F_3N_9O_{16}$ 1340.535
14&15	2 0.25 g, 0.228 mmol	1-(2-Pyrimidyl), piperazine 0.347 g, 2.28 mmol	0.136 g, 4.56 mmol	10/5	14 0.078 g, 26.89 15 0.050 g, 15.24	NA NA	14 $C_{64}H_{95}N_{11}O_{16}$ 1274.512 15 $C_{73}H_{107}N_{15}O_{16}$ 1450.773
16&17	2 0.3 g, 0.273 mmol	1-(4-Flurophenyl), piperazine 0.492 g, 2.73 mmol	0.163 g, 5.46 mmol	15/5	16 0.22 g, 62.41 17 0.086 g, 21.23	16 161 (dec) 17 103	16 $C_{66}H_{96}FN_9O_{16}$ 1290.527 17 $C_{77}H_{109}F_2N_{11}O_{16}$ 1482.763
18&19	2 0.25 g, 0.228 mmol	1-Phenyl piperazine 0.369 g, 2.28 mmol	0.136 g, 4.56 mmol	10/16	18 0.11 g, 37.98 19 0.1 g, 30.39	18 164 19 134	18 $C_{66}H_{97}N_9O_{16}$ 1272.537 19 $C_{77}H_{111}N_{11}O_{16}$ 1446.782
20	2 0.25 g, 0.228 mmol	Dibenzylamine 0.449 g, 2.28 mmol	0.136 g, 4.56 mmol	10/24	20 0.17 g, 57.12	20 160-161	20 $C_{70}H_{98}N_8O_{16}$ 1307.582
21	2 0.25 g, 0.228 mmol	1-Benzyl piperazine 0.401 g, 2.28mmol	0.136 g, 4.56 mmol	10/18	21 0.18 g, 61.47	21 154	21 $C_{67}H_{99}N_9O_{16}$ 1286.563
22	2 0.194g , 0.177 mmol	1-(2-Pyridyl) piperazine 0.288 g , 1.77	0.106 g, 3.54 mmol	10/6	22 0.14 g, 62.24	22 159-161	22 $C_{65}H_{96}N_{10}O_{16}$ 1273.524

Comp. No.	Starting Compound	Secondary Amine	Para-formal-dehyde	Dioxan (ml)/ React. time (hr.)	Comp.No. Yield (g , %)	M.P.(°C)	Mole.Formula/ Mole.Weight.
23&24	2 0.4 g, 0.364 mmol	1-(4-Methylphenyl) piperazine 0.288 g, 1.77 mmol	0.218 g, 7.28 mmol	15/20	23 0.19 g, 40.55 24 0.034 g, 6.33	23 140 24 166	23 $C_{67}H_{99}N_9O_{16}$ 1286.583 24 $C_{79}H_{115}N_{11}O_{16}$ 1474.835
25	2 0.3 g, 0.273 mmol	1-(4-Pyridyl) piperazine 0.445 g , 2.73 mmol	0.163 g, 5.46 mmol	15/7	25 0.207 g, 52.31	25 89	25 $C_{75}H_{109}N_{13}O_{16}$ 1448.457
26	2 0.35 g, 0.319 mmol	4 –Piperidino-piperidine 0.536 g, 3.19 mmol	0.191 g, 6.38 mmol	15/2.5	26 0.27 g, 66.33	26 87	26 $C_{66}H_{103}N_9O_{16}$ 1278.584
27&28	2 0.325 g, 0.296 mmol	1-(2,6-Dimethyl phenyl) piperazine 0.563 g, 2.96 mmol	0.177 g, 5.92 mmol	15/6	27 0.17 g, 44.17 28 g , 17.53	27 165 28 136	27 $C_{68}H_{101}N_9O_{16}$ 1300.590 28 $C_{81}H_{119}N_{11}O_{16}$ 1502.889
29&30	2 0.35 g, 0.319 mmol	1-(1-Phenylethyl) piperazine 0.607 g, 3.19 mmol	0.191 g, 6.38 mmol	15/8	29 0.13 g, 31.37 30 0.205 g, 42.80	29 142 30 110	29 $C_{68}H_{101}N_9O_{16}$ 1300.590 30 $C_{81}H_{119}N_{11}O_{16}$ 1502.889
31	2 0.35 g, 0.319 mmol	N-(ter.butyl) benzylamine 0.52 g, 3.19 mmol	0.191 g, 6.38 mmol	15/24	31 0.03 g, 7.39	NA	31 $C_{67}H_{100}N_8O_{16}$ 1273.565

Comp. No.	Starting Compound	Secondary Amine	Para-formal-dehyde	Dioxan (ml)/ React. time (hr.)	Comp.No. Yield (g , %)	M.P.(°C)	Mole.Formula/ Mole.Weight.
32&33	2 0.35 g, 0.319 mmol	N-(Isopropyl) benzylamine 0.476 g, 3.19 mmol	0.191 g , 6.38 mmol	15/6	32 0.13 g, 32.39 33 0.125 g, 27.61	32 145 33 103-105	32 $C_{66}H_{98}N_8O_{16}$ 1259.538 33 $C_{77}H_{113}N_9O_{16}$ 1420.784
34&35	Orn-5 & homo-Tyr-4-dibenzyl , MLD(3) 0.35 g, 0.294 mmol	Piperidine 0.250 g , 2.94 mmol	0.176 g , 5.88 mmol	30/31	34 0.17 g, 19.64 35 0.25 g, 26.88	34 NA 35 76-80	34 $C_{68}H_{100}N_8O_{16}$ 1285.576 35 $C_{74}H_{111}N_9O_{16}$ 1382.735
36&37	3 0.1 g, 0.084 mmol	Pyrrolidin 0.059 g , 0.84 mmol	0.0504 g , 1.68 mmol	10/3	36 0.021 g, 19.64 37 0.05 g, 43.89	36 NA 37 81-83	36 $C_{67}H_{98}N_8O_{16}$ 1271.549 37 $C_{72}H_{107}N_9O_{16}$ 1354.682
38&39	3 0.322 g, 0.271 mmol	4 –Methyl piperidine 0.268 g , 2.71 mmol	0.162 g , 5.42 mmol	15/16	38 0.09 g, 25.56 39 0.087 g, 22.76	38 135-137 39 87-90	38 $C_{69}H_{102}N_8O_{16}$ 1299.602 39 $C_{76}H_{115}N_9O_{16}$ 1410.789
40&41	3 0.422 g, 0.355 mmol	N-(α,α,α-Trifluro-m-tolyl) piperazine 0.817 g , 3.55 mmol	0.213 g , 7.1 mmol	20/6	40 0.04 g, 7.87 41 0.35 g, 58.92	40 155-160 41 172-173	40 $C_{74}H_{102}F_3N_9O_{16}$ 1430.659 41 $C_{86}H_{115}F_6N_{11}O_{16}$ 1672.903
42	3 0.25 g, 0.21 mmol	Dibenzylamine 0.414 g , 2.1 mmol	0.213 g , 7.1 mmol	15/18	42 0.130 g, 44.12	42 149-151	42 $C_{77}H_{104}N_8O_{16}$ 1397.706

Comp. No.	Starting Compound	Secondary Amine	Para-formal-dehyde	Dioxan (ml)/ React. time (hr.)	Comp.No. Yield (g , %)	M.P.(°C)	Mole.Formula/ Mole.Weight.
43&44	Orn-5-methoxy , MLD(4) 0.3 g, 0.293 mmol	1-(4-Flurophenyl) piperazine 0.528 g, 2.93 mmol	0.175 g , 5.86 mmol	15/5	43 0.19 g, 53.31 44 0.071 g, 16.99	43 191-192 44 110	43 $C_{60}H_{92}FN_9O_{16}$ 1214.429 44 $C_{71}H_{105}F_2N_{11}O_{16}$ 1406.665
45&46	4 0.4 g, 0.391 mmol	1-Phenyl piperazine 0.634 g , 3.91 mmol	0.234 g , 7.82 mmol	20/6	45 0.23 g, 49.13 46 0.05 g, 9.3	45 114 46 NA	45 $C_{60}H_{93}N_9O_{16}$ 1196.439 46 $C_{71}H_{107}N_{11}O_{16}$ 1370.684

(NA = Not Available)
(MLD = mulundocandin)

Procedure for the preparation of compounds 49 & 50:

To a stirred solution of mulundocandin 1 (4.8 g, 5.15 mmol) in anhydrous 1,4-dioxane (150 ml), under nitrogen atmosphere was added anhydrous methylthioglycolate (11.87 g, 111.83 mmol) and a catalytic amount of p-toluenesulfonic acid (0.338 g, 1.758 mmol) and the reaction mixture was stirred at ambient temperature for 1.5 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). TLC analysis after 1.5 hr. showed no starting compound. The reaction was quenched at 5-10 °C by the addition of saturated aqueous $NaHCO_3$ and evaporated to smaller volume (25 ml). The above mixture was diluted with water (250 ml), extracted with n-BuOH (3 x 150 ml), washed with water (200 ml) followed by brine (200 ml). Combined organic extract was dried over anhydrous Na_2SO_4, filtered and was concentrated in vacuum to give gummy product, which was then dissolved in a minimum amount of methanol (MeOH) (15 ml), adsorbed on silica gel (1:1 w/w), and was subjected to silica gel flash column chromatography. 0-15 % MeOH/$CHCl_3$ was used as 5 % step gradient elution. Evaporation of the appropriate fractions gave white compound 49 (3.171 g, 60.75 %) and 49 (0.885 g, 15.69 %).

Compound 49 :

Methyl-2-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-9-(11-methyltridecylcarboxamido)-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:1-/][1,4,7,10,13,16]hexaazacyclohenicosin-12-ylsulfanyl] acetate.

Partial ^{1}H NMR : 7.2 (d, 2H, 8.54 hz), 6.8 (d, 2H, 8.54 hz), 5.39 (br, 1H), 3.75 (s, 3H, OCH_3), 3.45, 3.65 (2 x d, 2H, 15.78 hz).

IR(KBr): 3350, 2920, 1730, 1660-1620br, 1520, 1440, 1385, 1230, 1075 cm^{-1}

ESI MS(ES+): for $C_{51}H_{81}N_7O_{17}S$

Calculated : 1096.291

Found :$(M+Na)^+$ = 1118.5 (base peak)

1074.6, 1044.7, 1012.6, 771.3, 589.2, 567.1.

UV(MeOH): λ_{max} pH: 206, 225, 277 nm (ε = 11990, 5769, 9428)

Compound 50 :

Methyl-2-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-2,11,15-trihydroxy-6-((1R)-1-hy- droxyethyl)-23-((1S)-1-hydroxy-2-(4-hydroxyphenyl)-2-methoxycarbonylmethylsulfanyl- ethyl)-20-hydroxymethyl-16-methyl-9-(11-methyltridecylcarboxamido)-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:1-/][1,4,7,10,13,16]hexaazacyclohenicosin-12-ylsulfanyl]- acetate.

Partial ^{1}H NMR : 7.25, 7.12 (2 x d, 2H, 8.55 hz), 6.8 (2 x d, 2H, 8.55 hz), 5.41 (br, 1H), 3.75 (s, 3H), 3.65, 3.8 (2 x s, 3H), 3.45, 3.64 (2 x d, 2H), 3.21-2.85 (m, 2H).

IR(KBr): 3300-3400 br, 2930, 1740(ester), 1680-1610 br, 1520, 1435, 1380, 1260, 1070 cm^{-1}

ESI MS(ES+): for $C_{54}H_{85}N_7O_{18}S_2$

Calculated : 1184.414

Found :$(M+Na)^+$ = 1206.6 (base peak)

1100.6, 966.5, 859.3, 808.5, 567.2.

UV(MeOH): λ_{max}: 204, 227 nm (ε = 9685, 2421)

Procedure for the preparation of compounds 51 & 52:-

To a stirred solution of mulundocandin 1 (2.3 g, 2.28 mmol) in anhydrous 1,4-dioxane (100 ml), under nitrogen atmosphere was added anhydrous thiophenol

(4.29 g, 38.95 mmol) and a catalytic amount of p-toluenesulfonic acid (0.23 g, 1.196 mmol) and the reaction mixture was stirred at ambient temperature for 3 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). The reaction workup and purification process were similar to that described for compounds 49 and 50. Yield of the white solid 51 (1.241 g, 49.44 %) and 52 (0.478 g, 17.57 %).

Compound 51 :
N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(4-hydro- xyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl -5,8,14,19,22,25-hexaoxo-12-phenylsulfanyl-perhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.
Partial ^1H NMR : 7.58 (m, 2H), 7.33 (t, 3H, 2.63 hz), 7.2 (d, 2H, 8.39 hz), 6.8 (d, 2H, 8.39 hz), 5.69 (br, 1H).
IR(KBr): 3400-3300br, 2940, 1670, 1630, 1525, 1460, 1390, 1250, 1075 cm^{-1}
ESI MS(ES+): for $C_{54}H_{81}N_7O_{15}S$
Calculated : 1100.326
Found :$(M+Na)^+$ = 1122.6 (base peak)
1078.7, 1012.5, 970.6, 808.5, 771.3, 567.3.
UV(MeOH): λ_{max}: 206, 228, 265 nm (ε = 36860, 22336, 4703)

Compound 52 :
N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-2,11,15-trihydroxy-6-((1R)-1-hydroxy- ethyl)-23-((1S)-1-hydroxy-2-(4-hydroxyphenyl)-2-phenylsulfanylethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxo-12-phenylsulfanylperhydrodia-zolo[2,1-c:2,1-/] [1,4,7, 10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.
Partial ^1H NMR : 7.58 (m, 2H),7.30 (t, 3H, 3.3 hz),7.18-7.25(m, 5H, homo-Tyr-4-SPh), 6.91 (d, 2H, 8.4 hz), 6.61(d, 2H, 8.4 Hz),5.69 (br, 1H).
IR(KBr): 3400-3300 br, 2940, 1680-1620 br, 1520, 1450, 1380, 1240, 1075 cm^{-1}
ESI MS(ES+): for $C_{60}H_{85}N_7O_{14}S_2$
Calculated : 1192.484
Found :$(M+Na)^+$ = 1214.6 (base peak)

1136.7, 466.5.

UV(MeOH): λ_{max}: 205, 255 nm (ε = 32415, 4892)

Compound 53 :

Methyl-2-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-9-(11-methyltridecylcarboxamido)-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:1-/][1,4,7,10,13,16]hexaazacyclohenicosin-12-ylsulfonyl] acetate.

To a stirred solution of thioether 48 (0.515 g, 0.47 mmol) in 70 ml of 1:1 acetonitrile/water at ambient temperature was added OXONE® (0.577 g, 0.94 mmol). After a period of 1 hr. TLC analysis (20 % MeOH/$CHCl_3$) showed conversion to a more polar product to be complete. The reaction mixture was evaporated under reduced pressure to smaller volume (25 ml). White sold precipitated out was filtered off, washed with water (25 ml) dried under high vacuum to yield nearly 90 % pure sulfone 52 (0.45 g, 84.90 %). This was used without purification for further reactions.(OXONE = $KHSO_5$, $KHSO_4$, K_2SO_4; 2:1:1).

Partial ^{1}H NMR : 7.18 (d, 2H, 8.58 hz), 6.8 (d, 2H, 8.58 hz), 5.6 (br, 1H), 3.92-4.08 (m, 2H, $SO_2CH_2CO_2CH_3$), 3.85 (s, 3H, -OCH_3).

IR(KBr): 3500-3400 br, 2920, 2890, 1680-1625 br, 1525, 1445, 1225, 1080 cm^{-1}

ESI MS(ES+): for $C_{51}H_{81}N_7O_{19}S$

Calculated : 1128.289

Found :$(M+Na)^+$ = 1150.6 (base peak)

1034.5, 1144.6, 1012.5, 968.5, 808.6, 771.4, 567.4.

UV(MeOH): λ_{max}: 208, 223, 276 nm (ε = 43326, 31366, 3587)

Compound 54 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-cyano-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/]-[1,4,7,10,13,16]hexaaza-cyclohenicosin-9-yl]-12-methyltetradecanamide.

A solution of ornithine-5-sulfone 52 (0.5 g, 0.443 mmol) and sodium cyanide (0.1 g, 2.04 mmol) in anhydrous N,N-dimethylformamide (10 ml), under nitrogen

atmosphere was stirred at ambient temperature for 1 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). The reaction mixture was diluted with water (150 ml), extracted with n-BuOH (3 x 100 ml), washed with water (150 ml) followed by brine (150 ml). Combined organic extract was dried over anhydrous Na_2SO_4, filtered and was concentrated in vacuum to give a crude product. This was then dissolved in a minimum amount of MeOH (5 ml), adsorbed on silica gel (1:1 w/w), and was subjected to silica gel flash column chromatography. 0-20 % MeOH/$CHCl_3$ was used as 5 % step gradient elution. Evaporation of the appropriate fractions gave ornithine-5-cyanocompound 54 (0.16 g, 35.55 %). Yield is calculated from nearly 90 % pure starting compound.

Partial ^1H NMR : 7.18 (d, 2H, 8.55 hz), 6.78 (d, 2H, 8.55 hz), 5.17 (br, 1H).

^{13}C NMR Spectrum :

177.08, 176.94, 174.72, 174.31, 174.17, 174.08, 173.56, 173.47, 172.98, 172.81, 172.20, 171.28, 170.73, 159.21, 133.70, 130.52, 130.24, 119.69, 118.80, 117.04, 77.41, 76.60, 72.12, 71.83, 70.65, 69.93, 69.64, 69.00, 68.83, 64.27, 63.89, 63.31, 63.08, 59.38, 59.18, 58.06, 57.04, 56.38, 54.70, 54.42, 54.21, 53.69, 53.43, 52.28, 46.13, 39.89, 39.37, 38.56, 37.63, 36.94, 36.45, 36.19, 31.19, 31.57, 31.37, 31.28, 31.14, 31.05, 28.97, 27.84, 27.55, 21.06, 20.45, 12.56, 12.19, 12.04.

IR(KBr): 3330-3400 br, 2910, 2320(CN peak), 1650, 1620, 1510, 1430, 1370, 1230, 1070 cm^{-1}

ESI MS(ES+): for $C_{49}H_{76}N_8O_{15}$

Calculated : 1017.178

Found :$(M+Na)^+$ = 1039.6 (base peak)

999.6, 995.5, 887.4, 567.4.

UV(MeOH):- λ_{max}: 205, 223, 276 nm (ε = 16989, 10046, 986)

Compound 55 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-aminomethyl-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxy- methyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

To a saturated solution of ammonia in anhydrous methanol (10 ml) was added 53 (0.1 g, 0.098 mmol) and a catalytic amount of Raney Nickel (0.03 g). The reaction

vessel (hydrogenation bottle, 250 ml) was evacuated by aspirator and thoroughly purged with hydrogen (three times). The resulting heterogeneous mixture was stirred under hydrogen atmosphere at 45 lb/in^2 pressure for 4 hr. TLC analysis (20 % methanol/$CHCl_3$) showed complete conversion to a more polar product. The catalyst was filtered off through celite and the filtrate was concentrated under vacuum to give a crude product, which was subjected to reverse-phase (5g, C-18) flash column chromatography eluting with 50-90 % acetonitrile/water as 10 % step gradient. Lyophilization of the appropriate fractions provided 55 (0.053 g, 52.79 %).
Partial ^{1}H NMR : 7.18 (d, 2H, 8.50 hz), 6.8 (d, 2H, 8.50 hz), 2.1 (m, 2H), iminol proton shifted upfield.
ESI MS(ES+): for $C_{49}H_{80}N_8O_{15}$
Calculated : 1021.210
Found :$(M+Na)^+$ = 1043.5 (base peak)
1019.4, 985.6, 852.8, 778.7, 760.7, 516.1, 392.4.
UV(MeOH): λ_{max}: 206, 225, 277 nm (ε = 29806, 26711, 6481)

Compound 56 :
N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(4-hydro- xyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-12-(2-morpholinoethylamino)-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/] [1,4,7, 10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.
To a stirred solution of ornithine-5-sulfone 52 (0.1 g, 0.089 mmol) in anhydrous 1,4-dioxane (10 ml), under nitrogen atmosphere was added 4-(2-aminoethyl) morpholine (0.495 g, 3.8 mmol) and the reaction mixture was stirred at 25-60°C for 1 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). The reaction work-up was similar to that described for compound 54. Crude product was purified by using reverse-phase (4 g, C-18) flash column chromatography eluting with 50-90 % acetonitrile/water as 10 % step gradient. Lyophilization of the appropriate fractions provided 56 (0.07 g, 70.5 %) Yield is calculated from nearly 90 % pure starting compound.
Partial ^{1}H NMR : 7.2 (d, 2H, 8.55 hz), 6.8 (d, 2H, 8.55 hz), 5.04 (br, 1H), 3.7-3.8 (m, 4H), 2.35-2.2 (m, 8H).

IR(KBr): 3300-3400 br, 2930, 1680-1620 br, 1520, 1435, 1380, 1260, 1070 cm^{-1}

ESI MS(ES+): for $C_{54}H_{89}N_9O_{16}$

Calculated : 1120.341

Found :$(M+Na)^+$ = 1142.6 (base peak)

1130.6, 540.3.

Compound 57 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-(1H-1,3-diazolo-1-yl)-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydro-diazolo[2,1-c:2,1-/][1,4,7,10, 13,16] hexaazacyclohenicosin-9-yl]-12-methyl-tetradecanamide.

To a stirred solution of ornithine-5-sulfone 53 (0.1 g, 0.089 mmol) in anhydrous 1,4-dioxane (10 ml), under nitrogen atmosphere was added imidazole (0.024 g, 0.356 mmol) and the reaction mixture was stirred at 25-60°C for 1 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). After one hour the reaction mixture was diluted with water (100 ml), extracted with n-BuOH (3 x 50 ml), washed with water (100 ml) followed by brine (100 ml). Combined organic extract was dried over anhydrous Na_2SO_4 and was concentrated in vacuum to give a crude product. The crude product was purified by using reverse-phase (5g, C-18) flash column chromatography eluting with 50-90 % acetonitrile/water as 10 % step gradient. Lyophilization of the appropriate fractions provided 57 (0.06 g, 64.03 %) Yield is calculated from nearly 90 % pure starting compound.

Partial ^1H NMR : 7.8 (s, 1H), 7.65 (br s, 2H), 7.18, (d, 2H, 8.55 hz),6.8(d, 2H, 8.55 hz), 5.30 (br s, 1H).

IR(KBr): 3350-3400 br, 2931, 1650 br, 1620, 1520, 1455, 1390, 1225, 1065 cm^{-1}

ESI MS(ES+) : for $C_{51}H_{79}N_9O_{15}$

Calculated : 1058.230

Found : (M^+) = 1058.6

1044.6, 1012.4, 968.5, 848.5, 771.3, 567.4

Note Starting compound (ornithine-5 and homo-tyrosine-4-disulfone mulundocandin) for the preparation of compounds 57, 58 and 59, was prepared from thioether 49 using the process outlined for preparation of compound 52.

Compound 58 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-cyano-23-((1S)-2-cyano-1-hydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaaza- cyclo henicosin-9-yl]-12-methyltetradecanamide.

Using the process outlined for the preparation of 53, a solution of ornithine-5 & homo-tyrosine-4-disulfone mulundocandin (0.5 g, 0.4 mmol) and anhydrous sodium cyanide (0.2 g, 4.08 mmol) in anhydrous N,N-dimethylformamide (10 ml), under nitrogen atmosphere was stirred at ambient temperature for 1 hr to yield dicyanomulundocandin 58 (0.19 g, 46.22 %).

Partial ^{1}H NMR : 7.2 (d, 2H, 8.22 hz), 6.85 (d, 2H, 8.22 hz), iminol proton shifted upfield.

IR(KBr): 3330-3400 br, 2910, 2320(CN peak), 1650, 1620, 1510, 1430, 1370, 1230, 1070 cm^{-1}

ESI MS(ES+): for $C_{50}H_{75}N_9O_{14}$

Calculated : 1026.189

Found :$(M+Na)^+$ = 1048.5 (base peak)

1004.2, 887.3.

Compound 59 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-azido-23-((1R)-2-azido-1-hydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaaza- cyclohenicosin-9-yl]-12-methyltetradecanamide.

Using the process outlined for the preparation of 54, a solution of ornithine-5 & homo-tyrosine-4-disulfone mulundocandin (0.2 g, 0.16 mmol), anhydrous sodium azide (0.104 g, 1.6 mmol) in anhydrous 1,4-dioxane (10 ml), was stirred at 25-50°C for 2 hr. Crude product was purified by using semi preparative HPLC. (semiprep RP-18 column, 250 x 16 mm, 10μ particle size, 70 % acetonitrile/water as a eluant, 8 ml/min. flow rate, λ = 220 & 270 nm). Lyophilization of the appropriate fractions provided 59 (0.115 g, 67.84 %). Yield is calculated from nearly 90 % pure starting compound.

Partial ^{1}H NMR : 7.28, 7.14 (2 x d, 2H, 8.88 hz), 6.83 (t, 2H, 8.88 hz), 5.39(d, 1H, 1.86 hz).

IR(KBr): 3300-3400 br, 2930, 2100(sharp), 1650, 1620, 1515, 1440, 1240, 1070 cm^{-1}

ESI MS(ES+): for $C_{48}H_{75}N_{13}O_{14}$

Calculated : 1058.194

Found : $(M+Na)^+$ = 1080.5

1037.6, 873.9, 816.6, 567.0.

UV(MeOH): λ_{max}: 206, 221, 275 nm (ε = 21163, 8266, 1985)

Compound 60 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-2,11,15-trihydroxy-6-((1R)-1-hydroxy- ethyl)-23-((1R,2R/S)-1-hydroxy-2-(4-hydroxyphenyl)-2-(2-morpholinoethyl-amino)ethyl)-20-hydroxymethyl-16-methyl-12-(2-morpholinoethylamino)-5,8,14,19,22,25-hexaoxoper- hydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradeca- namide.

Using the process outlined for the preparation of 54, a solution of ornithine-5 & homo-tyrosine-4-disulfonemulundocandin (0.2 g, 0.16 mmol), 4-(2-aminoethyl)morpholine (0.208 g, 1.6 mmol) in anhydrous 1,4-dioxane (10 ml), was stirred at 25-50°C for 2 hr. Crude product was purified by using semi preparative HPLC. (semiprep RP-18 column, 250 x 16 mm, 10μ particle size, 70 % acetonitrile/water as a eluant, 8 ml/min. flow rate, λ = 220 & 270 nm). Lyophilization of the appropriate fractions provided 60 (0.093 g, 43.89 %). Yield is calculated from nearly 90 % pure starting compound.

Partial ^{1}H NMR : 7.26 (t, 2H, 8.55 hz), 6.8 (d, 2H, 8.55 hz), 5.04 (br, 1H), 3.7-3.8 (m, 8H), 2.4-2.27 (m, 16H).

IR(KBr): 3300-3400 br, 2930, 1680-1620 br, 1520, 1435, 1380, 1260, 1070 cm^{-1}

ESI MS (ES+): for $C_{60}H_{101}N_{11}O_{16}$

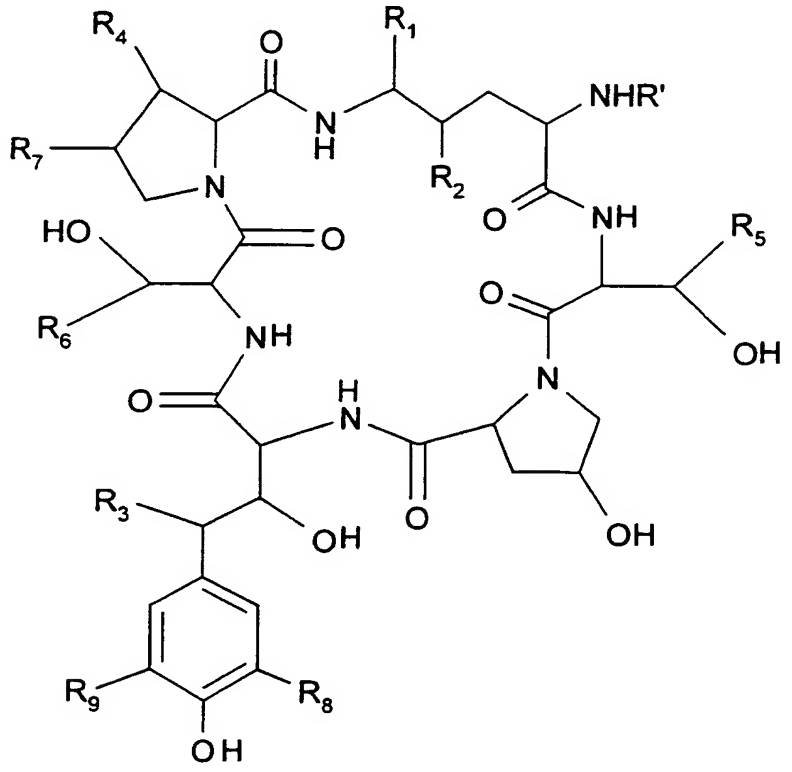
Calculated : 1232.516

Found : $(M+Na)^+$ = 1254.8 (base peak)

1133.6, 990.6, 946.4, 302.8.

Claims:

1. A cyclohexapeptide compound of the general formula I ;



I

wherein,

R^1 is C_1-C_{20} alkyl; C_9-C_{20} alkenyl; C_9-C_{20} alkoxyphenyl; an aryl group selected from: phenyl, biphenyl, terphenyl and naphthyl; C_1-C_{12} alkylpenyl, C_2-C_{12} alkenylphenyl, C_1-C_{12} alkoxyphenyl; linoleoyl; palmitoyl; 12-methylmyristoyl; 10,12-dimethylmyristoyl; or $-COC_6H_4(p)OC_8H_{17}$,

R_1 and R_3 are independently -OH; -CN; $-CH_2NH_2$; $-N_3$; aryl; substituted aryl; heterocyclyl and substituted heterocyclic with 1-3 of the same or different heteroatoms; aminoalkylamino; mono or di-substituted linear or cyclic aminoalkylamino; -OR, wherein, R is C_1-C_{12} alkyl; substituted alkyl of the type $-(CH_2)_n$-X, where n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2 or a heterocyclic and where Y is C_1-C_6 linear or branched alkyl; C_2-C_{12}-alkenyl; aryl; fused aryl; substituted aryl; a heterocyclic containing 1-3 heteroatoms; mono or di-

substituted aminoalkyl; or a hydroxy protecting group; and R_3 may additionally be imidazolyl.

R_2 and R_4 are independently -H or –OH;

R_5 is -H or $-CH_3$.

R_6 is -H, $-CH_3$ or $-CH_2CONH_2$.

R_7 is -H, $-CH_3$ or -OH.

R_8 and R_9 are independently -H or $-CH_2$-Sec.amine in which the sec.amine is attached to $-CH_2$ through its N linkage;

and its pharmaceutically acceptable salts.

2. A compound of the formula I as claimed in claim 1 wherein R_1 is –OH or OR, and R_3 is –OH, -OR or imidazolyl wherein R in each case is C_1-C_{12} alkyl , substituted alkyl of the type $-(CH_2)_n$-X, where n is 1-5, X is Cl, Br, I, COOY, CN, NH_2 or a heterocyclic and Y is a C_1-C_6 linear or branched alkyl; -C_2-C_{12}-alkenyl; ary; fused aryl; substituted aryl; a heteroaryl containing 1-3 heteroatoms; a heterocyclic containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group.

3. A compound of the formula I as claimed in claim 1 or claim 2 wherein R^1 is linoleoyl, palmitoyl, 12-methylmyristoyl, 10, 12-dimethylmyristoyl or – $COC_6H_{4(p)}OC_8H_{17}$.

4. A compound of the formula I as claimed in claim 1, 2 or 3, wherein to the nitrogen atom of the secondary amine are attached the same or different groups selected from: C_1-C_{12} alkyl, C_2-C_{12} alkenyl, aryl, substituted aryl, alkylaryl and substituted alkylaryl, or the nitrogen atom of the secondary amine is part of a heterocyclic group, optionally substituted by one or more of: C_1-C_6 alkyl, C_1-C_6 alkenyl, aryl, amino, nitro and halogen, or a fused heterocyclic group, whereby the heterocyclic group contains 1-3 of the same or different heteroatoms.

5. A compound of the formula I as claimed in any one of the preceding claims, wherein the secondary amine is selected from: piperidine, pyrrolidine, 4-methylpiperidine, morpholine, dimethylamine, diisopropylamie, 4-piperidino-piperidine, piperazine, 1-methylpiperazine, 1-(2-fluorophenyl)piperazine, 1-(2-chlorophenyl)piperazine, 1-(2-pyrimidyl)piperazine, 1-(4-fluorophenyl)piperazine, N-(α,α,α-trifluoro-m-tolyl)piperazine, 1-phenylpiperazine, 1-benzylpiperazine, 1-(2-pyridyl)piperazine, 1-(4-pyridyl)piperazine, 1-(4-methylphenyl) piperazine, 1-(2,6-dimethylphenyl)piperazine, 1-(1-phenylethyl)piperazine, dibenzylamine, N-(tert-butyl)benzylamine and N-(isopropyl)benzylamine.

6. A compound of the formula I as claimed in claim 1, wherein R^I is 12-methylmyristoyl, R_1 and R_3 are independently -OH, -CN, $-CH_2NH_2$, $-N_3$, aryl, substituted aryl, heterocyclyl and substituted heterocyclyl having 1-3 of the same or different heteroatoms, aminoalkylamino, or mono or di-substituted linear or cyclic aminoalkylamino, R_5 and R_7 are both $-CH_3$, R_6 is –H, and R_8 and R_9 are both –H.

7. A pharmaceutical composition comprising an effective amount of the compound of the formula I or a pharmaceutically acceptable salt thereof as claimed in any one of the preceding claims, and a pharmaceutically acceptable carrier.

8. A compound of the formula I as claimed in any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof for use as an anti-fungal agent.

9. A process for the production of a compound of the general formula I as claimed in claims 1-5 , comprising the steps of:

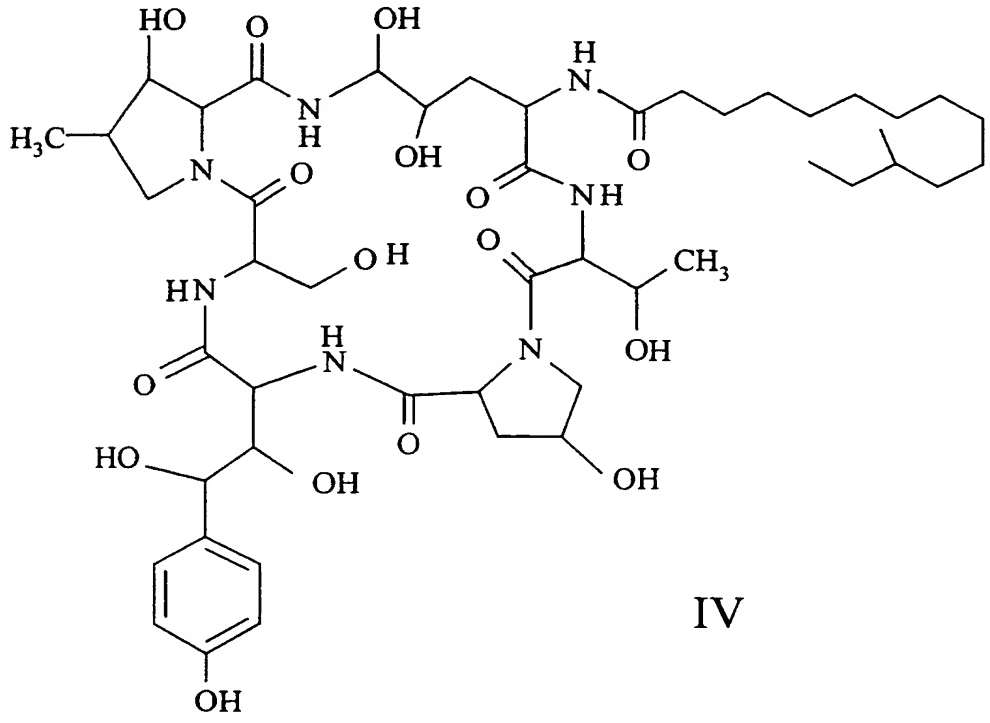
   a) reacting a cyclohexapeptide compound of the formula I, wherein R^I, R_2, R_4, R_5, R_6 and R_7 are as defined in claim 1, 2 or 3 , R_1 and R_3 are both –OH, and R_8 and R_9 are -H , with an alcohol in the presence of an acid in an aprotic solvent at a temperature ranging from 0°C to 60° to obtain the corresponding cyclohexapeptide derivative of the formula I wherein R^I, R_2,

R_4, R_5, R_6 and R_7 are as defined in claim 1, 2 or 3, R_1 and R_3 are independently –OH or –OR such that at least one of R_1 or R_3 is -OR, wherein R is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, fused aryl, substituted aryl, a heterocyclyl containing 1-3 heteroatoms, mono or di-substituted aminoalkyl, or a hydroxy protecting group, and R_8 and R_9 are -H;

b) reacting the compounds obtained in step (a) with a secondary amine in presence of paraformaldehyde in an aprotic solvent at a temperature ranging from 60°C to 150°C to yield the desired compound of formula I, isolating and purifying the resulting compound of formula I from the reaction mixture in a known manner and if desired, converting the compound of formula I into its pharmaceutically acceptable salt in a known manner.

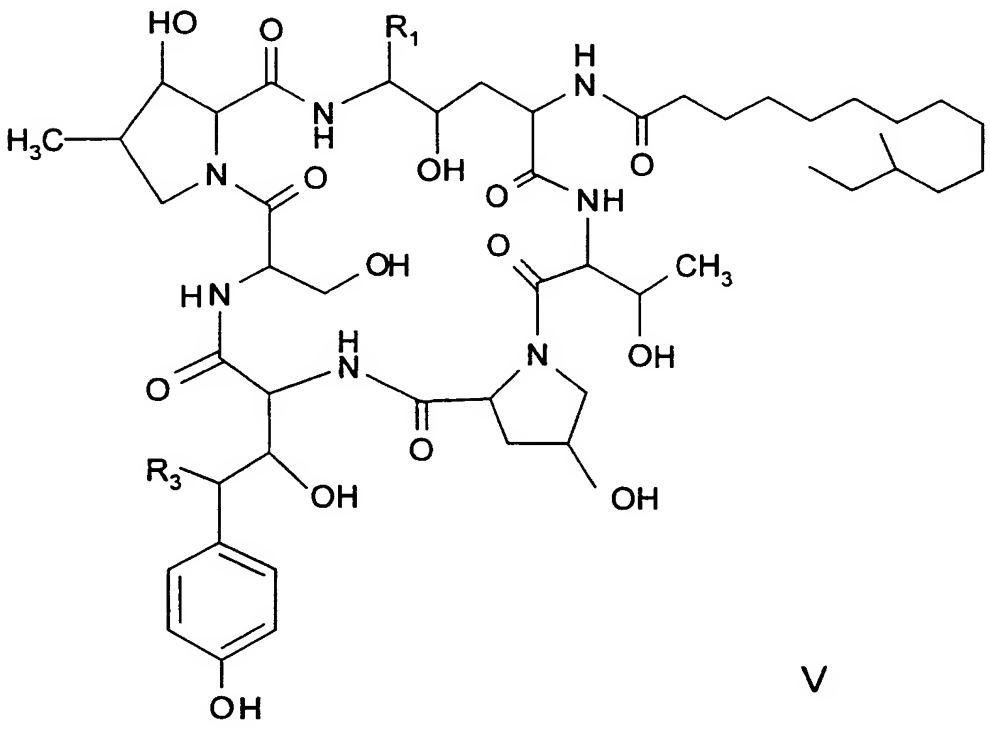
10. A process for the preparation of a cyclohexapeptide compound of the formula I as claimed in any one of claims 1 to 6, comprising the steps of :

a) reacting mulundocandin of the following formula IV,



IV

with a nucleophile in presence of an acid in an aprotic solvent at a temperature ranging from 0°C to 60° to obtain the corresponding cyclohexapeptide derivative of formula V;



V

wherein R_1 and R_3 are –OH or –SR such that at least one of R_1 or R_3 is -SR wherein R in each case is C_1-C_{12} alkyl, substituted alkyl of the type -$(CH_2)_n$-X, wherein n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2, or a heterocyclic, Y is C_1-C_6 linear or branched alkyl chain; C_2-C_{12} alkenyl; aryl; fused aryl; substituted aryl;

a heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group ;

b) reacting the compounds of formula V as obtained in step (a) with an oxidising agent in an aqueous medium at a temperature ranging from 20°C to 60°C to obtain the corresponding sulfones (VI), wherein R_1 and R_3 are –OH or -S

(O_2)R, such that at least one of R_1 or R_3 is $-SO_2R$, wherein R is a C_1-C_{12} alkyl, substituted alkyl of the type $-(CH_2)_n$-X, wherein n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2, a heterocyclic, Y is a C_1-C_6 linear or branched alkyl chain; C_1-C_{12} alkenyl; aryl; fused aryl; substituted aryl; a heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group;

c) reacting the sulfone (VI) obtained in step (b) with a nucleophile in a solvent at a temperature ranging from 20°C to 60°C to obtain the desired compound of the formula I, isolating and purifying the resulting compound of the formula I from the reaction mixture in a known manner and if desired, converting the compound of formula I into its pharmaceutically acceptable salt in a known manner.